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(54) **IL-2 receptor gamma chain molecule.**

(57) The present invention relates to an IL-2 receptor  $\gamma$  chain molecule, a DNA-sequence encoding the IL-2 receptor  $\gamma$  chain molecule, a vector possessing said DNA-sequence, a cell transformed with said vector, a method for the production of an IL-2 receptor  $\gamma$  chain molecule by culturing of said cell, an immune response regulatory agent comprising an IL-2 receptor  $\gamma$  chain molecule and an antibody to an IL-2 receptor  $\gamma$  chain molecule.

Both the IL-2 receptor  $\gamma$  chain molecule and the antibody to the IL-2 receptor  $\gamma$  chain molecule are very useful immune response regulatory agents.

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The present invention relates to an IL-2 receptor  $\gamma$  chain molecule which directs the transduction of signals from IL-2, the human IL-2 receptor  $\gamma$  chain, a DNA sequence encoding an IL-2 receptor  $\gamma$  chain molecule, a vector including said DNA sequence, a cell transformed with said vector, a method for the production of an IL-2 receptor  $\gamma$  chain molecule by culturing of said cell, an immune response regulatory agent comprising an IL-2 receptor  $\gamma$  chain molecule, a method for the detection or assay of the gene encoding an IL-2 receptor  $\gamma$  chain molecule, an antibody capable of binding to an IL-2 receptor  $\gamma$  chain molecule, an immune response regulatory agent comprising said antibody, and a method for detection or assay of an IL-2 receptor  $\gamma$  chain molecule by use of said antibody.

The existence of the present human IL-2 receptor  $\gamma$  chain molecule became known for the first time by the present invention. It is a substance useful for the clarification of IL-2/IL-2 receptor system and the development of a method for therapy or diagnosis of diseases due to immunopathy.

#### DESCRIPTION OF THE PRIOR ART

IL-2 is a protein produced by helper T-cells, which is a very important factor for biophylaxis, and is known to be involved in growth and differentiation induction of killer T-cells and to act on a variety of immunocompetent T-cells including B cells, macrophages, natural killer (NK) cells and lymphokine-activated killer (LAK) cells in the body (Science, 240, p. 1169, 1988).

Diseases known generically as autoimmune diseases are characterized by an attack of auto antibodies on self-components or by an attack of T-cells which attack the self, and most of them are known to be intractable ones of unknown etiology. For not a few of these autoimmune diseases, excessive or disordered production of IL-2 is considered to be one of the main factors causing aggravation of the condition.

In addition, prevention of the rejection of a transplant is understood to lead to success in organ transplantation, and the main mechanism of rejection is presumed to be the attack on the transplant by killer T-cells which have been activated by IL-2 (Transplantation Proceedings, 15, p. 264, 1983).

Incidentally, the physiological activity of IL-2 is known to be exerted through a receptor on the surface of effector cells which combines with IL-2 specifically. In the past, the IL-2 receptor present on activated T-cells was thought to include three types of different binding affinities for IL-2, i.e. high affinity binding ( $K_d = 10^{11}/M$ ), intermediate affinity binding ( $K_d = 10^9/M$ ) and low affinity binding ( $K_d = 10^8/M$ ).

In 1984 a gene for a receptor molecule of 55 kd was isolated which is now called the  $\alpha$  chain (Nature, 311, p. 626, 1984; and Nature, 311, p. 631, 1984). A genetic experiment for transfection of the cDNA for the present receptor into a eucaryocyte revealed that the  $\alpha$  chain can be a low affinity receptor by itself, and that it is a molecule required for the formation of a functional high affinity receptor (Nature, 318, p. 467, 1985; Journal of Experimental Medicine, 162, p. 363, 1986; and Nature, 320, p. 75, 1986). However, because of the lack of the signal transduction region in the isolated  $\alpha$  chain cDNA, another molecule has been believed to exist which is involved in the formation of a high affinity receptor and in the signal transduction.

Thereafter another gene for a receptor molecule of 75 kd was isolated, which is now called the  $\beta$  chain (Science, 244, p. 551, 1989), and the experiment for transfection of the gene into lymphoid cells confirmed that a functional intermediate affinity receptor is formed only with the  $\beta$  chain, and that simultaneous transfection of the genes for  $\alpha$  and  $\beta$  chains produces a functional high affinity receptor. These results have led us to the conclusions that a low affinity receptor consists of the  $\alpha$  chain only, whereas an intermediate affinity receptor consists only of the  $\beta$  chain, that association of  $\alpha$  and  $\beta$  chains through a noncovalent binding forms a high affinity receptor, and that the signal transduction occurs only when both intermediate and high affinity receptors are combined.

The structure of the  $\beta$  chain estimated on the basis of the sequence of the cDNA for the  $\beta$  chain of the IL-2 receptor includes a cytoplasmic region of 286 amino acid residues which is large enough to bear the signal transduction, but, nevertheless, no amino acid sequence homology was found which suggests a structural relationship with known signal transduction molecules, such as tyrosine kinase. In addition, no binding to IL-2 occurred in the experiment for the gene transfection in the case where fibroblasts, i.e. nonlymphoid cells, were used instead of lymphoid cells (Science, 244, p. 551, 1989). Simultaneous transfection of the genes for the  $\alpha$  and  $\beta$  chains certainly succeeded in the formation of a high affinity receptor in the same manner as in the case where a lymphoid cell was used, but was unsuccessful in internalising the IL-2 signal and forming a receptor with complete function (Journal of Immunology, 145, p. 2177, 1990).

These facts suggest the necessity of somewhat modifying the  $\beta$  chain itself or of the presence of a molecule other than  $\alpha$  and  $\beta$  chains which has some interactions with the  $\beta$  chain, in order that the  $\beta$  chain acquires ability to bind to IL-2 by itself, acquires ability of signal transduction and for the formation of a

functional, complete receptor. The presence of an intrinsic component in lymphoid cells satisfies this necessity. On the other hand, fibroblasts, which are nonlymphoid cells, do not satisfy this necessity.

According to recent researches, the comparison of the number of intermediate affinity binding sites of IL-2 with the number of the binding sites of the  $\beta$  chain of the IL-2 receptor in the case of NK cells in the peripheral blood from a patient who received treatment with IL-2 revealed that the binding site number of IL-2 was far less (Journal of Experimental Medicine, 172, p. 1101, 1990). According to experiments for chemical cross-linking with IL-2 using cells in which a high affinity IL-2 receptor was expressed, various molecules were reported to be able to form a complex with IL-2, including those of a molecular weight of 22 kd or 40 kd (proceedings of the National Academy of Sciences USA, 87, p. 11, 1990), that of m.w. 64 kd (International Immunology, 2, p. 477, 1990), that of m.w. 70 kd (Proceedings of the National Academy of Sciences USA, 84, p. 2002, 1987; and Nature, 327, p. 518, 1987), that of m.w. 95 kd (Proceedings of National Academy of Sciences USA, 84, p. 7246, 1987), that of m.w. 100 kd (Proceedings of the National Academy of Sciences USA, 87, p. 4869, 1990), and that of m.w. 95-100 kd (Journal of Immunology, 145, p. 155, 1990). Eventually, discussion as to the existence of molecules other than the  $\alpha$  and  $\beta$  chains are in a state of chaos to such an extent that it has not yet been concluded whether a third molecule actually exists. Thus, a structural elucidation of the IL-2 receptor has been made impossible.

Investigation and exact understanding of the mechanism of transduction of signals of IL-2 which plays a major role in the immune response are also required for a clarification of the pathogenetic mechanism and therapy of the diseases mentioned above. For this, first it is necessary to draw a definite conclusion as to whether a third IL-2 receptor molecule exists which directs the signal transduction as a constituent molecule of the IL-2 receptor (hereunder referred to as the IL-2 receptor  $\gamma$  chain molecule), and then the IL-2/IL-2 receptor system should be clarified indirectly on a molecular level.

To date, however, although reports have suggested the existence of an IL-2 receptor  $\gamma$  chain molecule, various views have been presented for the substance of the IL-2 receptor  $\gamma$  chain. Actually its molecular weight has not been determined yet, and it is entirely unclear even as to its existence, much more concerning the role of the third molecule for exertion of the function of IL-2. Accordingly, now worldwide competitions are being made for the isolation of its gene, expression of the protein molecule and analysis of the function of the molecule, leading to the finding of a direct evidence for the existence of the  $\gamma$  chain molecule.

### SUBJECT MATTER OF THE INVENTION

Briefly, the object of the present invention is to provide a IL-2 receptor  $\gamma$  chain molecule, particularly human IL-2 receptor  $\gamma$  chain molecule, which directs transduction of signals from human IL-2, a human IL-2 receptor  $\gamma$  chain molecule, a gene encoding the IL-2 receptor  $\gamma$  chain molecule, a vector containing said gene, a cell transformed with said vector, a method for the production of a IL-2 receptor  $\gamma$  chain molecule by culturing said cell, an immune response regulatory agent comprising a IL-2 receptor  $\gamma$  chain molecule, a method for detection or assay of the gene encoding a IL-2 receptor  $\gamma$  chain molecule, an antibody capable of binding to an IL-2 receptor  $\gamma$  chain molecule, an immune response regulatory agent which comprises said antibody, and is effective to cure autoimmune diseases and to prevent graft rejection, and a method for the detection or assay of an IL-2 receptor  $\gamma$  chain molecule by using said antibody.

In order to accomplish the subject matter previously described, the inventors of the present invention carried out diligent and extensive studies. As a result, there was found the desired human IL-2 receptor  $\gamma$  chain molecule, a DNA sequence said human IL-2 receptor  $\gamma$  chain molecule, a plasmid vector possessing said DNA sequence, a cell transformed with said vector, a method for the production of human IL-2 receptor  $\gamma$  chain molecule, which comprises culturing of said transformed cell, and an antibody capable of binding to human IL-2 receptor  $\gamma$  chain molecule, and thus the present invention has been accomplished. Hereunder, a detailed explanation will be given regarding the present invention. First, for separation and purification of the human IL-2 receptor  $\gamma$  molecule from the cell surface, MOLT4 cells, a human T lymphocyte cell line, were employed, wherein the  $\alpha$  and  $\beta$  chains of the IL-2 receptor are thought not to have been expressed, but high level expression is thought to have been established for the  $\gamma$  chain. Then, cells into which the cDNA for the  $\beta$  chain was transfected with a vector for expression in eucaryotes are prepared (hereunder referred to as MOLT  $\beta$  cells).

Here, as long as the IL-2 receptor  $\beta$  and  $\gamma$  chains are expressed, any human cell may be used for the separation and purification of the IL-2 receptor  $\gamma$  chain molecule. This may also be accomplished by use of other cells than human, which satisfy the above requirement, thus enabling the separation and purification of the IL-2 receptor  $\gamma$  chain molecule from other species. A cell on which only the  $\gamma$  chain is originally exposed is used as a host. Transfectants having incorporated an expression vector containing the cDNA for

the  $\beta$  chain may be used. It is added for confirmation only that any human cells other than MOLT4 cells on which only the  $\gamma$  chain is expressed, may be used.

Incidentally, the method for the genetic transduction includes electroporation, potassium phosphate coprecipitation, DEAE dextran, lipofection and any other method with which the desired gene may be transfected (Molecular Cloning, 3rd edition). Electroporation is preferably employed because it provided efficient transfection of the cDNA for the  $\beta$  chain.

Next, MOLT  $\beta$  cells are solubilized after their reaction with human recombinant IL-2. The solubilizing agent available for this use is a detergent such as NONIDET P-40, TRITON X-100, etc.

Of course, other detergents may be used.

From this solubilized cell fraction is separated a complex consisting of the three molecules: i.e. the IL-2 molecule, the IL-2 receptor  $\beta$  chain molecule and the  $\gamma$  chain molecule. Any other method may be used for the separation, but usually affinity chromatography is preferred.

The affinity chromatography may be carried out by immobilizing an anti-human IL-2 antibody or anti-human IL-2 receptor  $\beta$  chain antibody on a carrier. Here, the anti-human IL-2 antibody or anti-human IL-2 receptor  $\beta$  chain antibody should be such that it does not prevent binding of the respective other antibody, that is, an antibody which does not recognize the respective binding site itself should be used. The kind of animal used as the antibody source does not matter. Further, the antibody may be a polyclonal one, but a monoclonal antibody is recommended.

The supporting agent on which the antibody is immobilized includes agarose gel, polyacrylamide gel or the like, and embodiments of the activating agent to be used includes cyanogen bromide (in the case of agarose gel) and glutaraldehyde (in the case of polyacrylamide gel). Needless to say, the above listed embodiments are only examples of the supporting agent and activating agent, and others may be used.

We conducted earnest and extensive research and prepared many monoclonal anti-IL-2 receptor  $\beta$  chain antibodies. We conducted the selection on antibodies which do not prevent binding of IL-2 to the IL-2 receptor  $\beta$  chain. Then, of the selected ones was selected the most appropriate antibody for the separation and purification of a complex consisting of the IL-2 molecule, the IL-2 receptor  $\beta$  chain molecule and the  $\gamma$  chain molecule, which antibody was subjected to affinity chromatography for separation and purification of an adequate amount of the complex.

Actually, antibody-bound beads and a solubilized cell fraction were mixed for reaction, then the beads were washed thoroughly to elute the three molecules bound to the beads: the IL-2 molecule, the IL-2 receptor  $\beta$  chain molecule and the  $\gamma$  chain molecule. As the elution agent, an acid, an alkali, a protein denaturant, a salt at a high concentration, an ionic detergent, an organic solvent, etc. may be used. In the case where polyacrylamide gel electrophoresis is conducted after the elution for separation of the three molecules, urea or the like is preferred since it has little influence on the electrophoresis.

Next, the eluate is subjected to electrophoresis to separate the IL-2 receptor  $\gamma$  chain molecule. Any electrophoresis including SDS polyacrylamide gel electrophoresis, isoelectric focusing and so forth, may be carried out as long as the three components are separated. However, two dimensional electrophoresis (isoelectric focusing for the first, and SDS electrophoresis for the second) is preferably effected to ensure complete separation.

After electrophoresis, a protein containing the IL-2 receptor  $\gamma$  chain molecule is electrically transferred from the polyacrylamide gel to a polyvinylidene difluoride (PVDF) membrane, and the site on which the IL-2 receptor  $\gamma$  chain molecule is transferred to is cut off. Here, in order to identify beforehand the site on which the IL-2 receptor  $\gamma$  chain molecule is transferred to, it is recommended to use another gel prepared under the same conditions, subject a portion of the elution fraction to electrophoresis under the same conditions and determine the respective site by protein staining.

Thereafter, the cut-off membrane carrying the transferred IL-2 receptor  $\gamma$  chain molecule is subjected to a vapor phase amino acid sequencer to determine the amino acid sequence from the N-terminus of the IL-2 receptor  $\gamma$  chain molecule. In this connection, the N-terminal amino acid sequence of the IL-2 receptor  $\gamma$  chain molecule was finally determined on the basis of the information from both, the above mentioned amino acid analysis and the sequence of the cDNA, and is listed as Sequence Identifying No. 8 in the Sequence Listings.

The present invention is the first success in the world of the purification of the human IL-2 receptor  $\gamma$  chain molecule which is substantially free from the other human proteins and of the determination of the amino acid sequence of its N-terminus.

On the basis of the determined amino acid sequence, all possible DNA sequences were deduced which were thought to correspond to it, and 4 mixtures of DNA oligomers of the N-terminal (5'-end) 17mer (corresponding to oligomers Nos. 1-4 in Fig. 1) and 2 mixtures of DNA oligomers of the C-terminal (3'-end) 22mer (of complementary sequences, corresponding to oligomers Nos. 5, 6 in Fig. 1) were designed and synthesized

with a DNA synthesizer. Here, the sites of the oligomers to be designed are not limited to these, and any site is available so far as the interstitial distance between the oligomers is over a certain level (around 15mer), and the lengths of the oligomers may be any of 15mer or more, provided that, for the 3'-end primer, the complementary sequence to the original must be designed in the direction from the 3'-end to the 5'-end.

Separately from the above, messenger RNA is prepared from MOLT  $\beta$  cells, and an oligo dT or random hexamer is used as a primer to prepare cDNA and a cDNA library. Any cell on which the human IL-2 receptor  $\gamma$  chain molecule is expressed may be used for collection of the messenger RNA (mRNA).

Incidentally, the preparation of the messenger RNA may be performed with an oligo dT cellulose column after the entire RNA fraction is harvested according to the guanidine thiocyanate method (Biochemistry, 13, p. 2633, 1974). A phage vector such as  $\lambda$ gt10,  $\lambda$ gt11 or  $\lambda$ ZAPII or a plasmid vector such as pBR or pUC may be used to prepare the cDNA library.

With the prepared cDNA a polymerase chain reaction (PCR) (Science, 230, p. 1350, 1985) was carried out using the above synthesized DNA oligomer as a primer and Taq polymerase, then the amplified cDNA was recovered.

The thus recovered, amplified cDNA was labelled with  $^{32}\text{P}$  for the preparation of a probe, and a clone containing the cDNA for the IL-2 receptor  $\gamma$  chain was harvested from the cDNA library mentioned above, and its base sequence was determined by the dideoxy method (Science, 214, p. 1205, 1981).

The base sequence of the IL-2 receptor  $\gamma$  chain molecule and its structure deduced from said base sequence are shown as Sequence Identification No. 3 in the Sequence Listings. This IL-2 receptor  $\gamma$  chain molecule was found to have an open reading frame consisting of 369 amino acids, of which 22 amino acids represent a signal sequence, and 347 amino acids correspond to a mature type of the polypeptide.

That is, in the sequence of the Sequence Identification No. 3 in the Sequence Listings, the sequence from the -22nd Met to the -1st Gly corresponds to the signal peptide. The signal peptide encoding gene is from ATG corresponding to the -22nd Met to GGG corresponding to the -1st Gly.

In turn, the mature type of the polypeptide corresponds to from the 1st Leu to the 347th Thr in Sequence Identification No. 3 in the Sequence Listings. The sequence from CTG corresponding to the 1st Leu to ACC corresponding to the 347th Thr is a gene which codes for the mature type of the polypeptide.

In addition, Sequence Identification No. 4 lists the amino acid sequence and the corresponding base sequence of a preform consisting of (1) the mature type of the polypeptide and (2) the signal sequence attached thereto, while the amino acid sequence and the corresponding base sequence of the mature type of the polypeptide are shown in the Sequence Identification No. 5 in the Sequence Listings.

It was revealed that, in the mature type of the polypeptide shown in the Sequence Identification No. 3 in the Sequence Listings, the section from the 1st Leu to the 232nd Asn represents an extracellular region, the one from the 233rd Pro to the 261st Leu represents a transmembrane region, and the one from the 262nd Glu to the 347th Thr represents an intracellular region.

Here, in order to confirm that the cDNA for the IL-2 receptor  $\gamma$  chain molecule is the very cDNA which encodes a functional IL-2 receptor  $\gamma$  chain molecule, the present cDNA was linked with an expression vector for expression in eucaryotes. After that, (1) a cDNA for the IL-2 receptor  $\gamma$  chain alone, (2) for the  $\beta$  chain alone, (3) for  $\beta$  and  $\gamma$  chains simultaneously, (4) for  $\alpha$  and  $\beta$  chains simultaneously, or (5) for the IL-2 receptor  $\alpha$ ,  $\beta$  and  $\gamma$  chains was transfected at the same time into a human cell where none of the IL-2 receptor  $\alpha$ ,  $\beta$  and  $\gamma$  chains was expressed. Any expression vector may be used which enables expression in eucaryotes, and, for example, the early promoter vector from simian virus 40 may be utilized.

The cell actually used for the genetic transfection was mouse L929, but, needless to say, other cells may also be used. The same genetic transfection method as the above may be used for other ones. Incidentally, the mouse L929 cell transfected with the cDNA for the IL-2 receptor  $\gamma$  chain (hereunder referred to as L $\gamma$ -4) has been deposited with Fermentation Research Institute, Agency of Industrial Science and Technology (Deposit No.: FERM BP-4199). Next, the cells transfected with the respective cDNA were measured for their ability to bind IL-2, binding affinity and internalizing ability. The results of the functional analysis of the present gene product revealed that transfection of only the  $\beta$  chain cDNA failed to provide IL-2 binding, simultaneous transfection of cDNAs for the  $\beta$  and the  $\gamma$  chains provided intermediate affinity as to binding to IL-2 and internalization of the IL-2 signal. Also, with cDNAs for the  $\alpha$  and the  $\beta$  chains brought about pseudo high affinity binding, but internalization of the IL-2 signal did not occur, whereas high affinity binding of IL-2 and internalization of the IL-2 signal was accomplished when  $\alpha$ ,  $\beta$  and  $\gamma$  chains were transfected at the same time.

In other words, for the first time it was proven that the  $\gamma$  chain first found according to the present invention is another constituent of the IL-2 receptor in addition to the  $\alpha$  chain of 55 kd and the  $\beta$  chain of 75 kd and is involved in signal transduction. Furthermore, for the first time the present gene product was revealed to be

the IL-2 receptor  $\gamma$  chain molecule which is indispensable for exerting the functions of IL-2.

Description will be made hereunder of a method for the production of the IL-2 receptor  $\gamma$  chain molecule by genetic engineering.

For the production of the present IL-2 receptor  $\gamma$  chain molecule, expression may be effected using, as the host, an eucaryote such as CHO cells, mouse L929 cells or the like or a procaryote including E. coli. Here, appropriate choice of an expressible vector depending on each host may be made. Usually an eucaryote is a better host for the expression of the IL-2 receptor  $\gamma$  chain molecule than a procaryote.

Now, when the mature type of the IL-2 receptor  $\gamma$  chain molecule which has the amino acid sequence shown in the Sequence Identification No. 5 in the Sequence Listings is intended to be produced, a gene may be used which corresponds to the amino acid sequence shown in the Sequence Identification No. 4 in the Sequence Listings. More particularly, a gene constructed by attaching a stop codon to a gene which codes for the amino acid sequence from the -22nd Met to the 347th Thr shown as the Sequence Identification No. 4 in the Sequence Listings may be used. Here, the base sequence of the gene is not limited to any particular one so far as it corresponds to the amino acid sequence listed in the Sequence Identification No. 4 in the Sequence Listings. Therefore, a natural one (cDNA sequence), or any gene prepared by synthesis may be employed.

Nevertheless, the use of the gene listed in the Sequence Identification No. 4 in the Sequence listings is preferred. Here, the gene listed in the Sequence Identification No. 4 in the Sequence Listings is the cDNA for the IL-2 receptor  $\gamma$  chain molecule.

For confirmation only, no trouble is caused by use of the gene listed in the Sequence Identification No. 4 in the Sequence Listings because the sequence comprises a stop codon, TGA, whereas attention has to be paid to putting a stop codon after the codon corresponding to the 347th Thr if a synthetic gene is employed. In the case of the production of the mature type of the IL-2 receptor  $\gamma$  chain molecule which possesses the amino acid sequence listed in Sequence Identification No. 5 in the Sequence Listings, using a procaryote such as E. coli, the gene encoding the amino acid sequence listed as the Sequence Identification No. 5 in the Sequence Listings should be inserted between the initiation codon ATG and an appropriate stop codon. Of course, also for this case, the gene encoding the amino acid sequence listed as the Sequence Identification No. 5 in the Sequence Listings may be used as a base sequence other than the natural one as Sequence Identification No. 5 in the Sequence Listings.

The use of the natural sequence shown in the Sequence Identification No. 5 in the Sequence Listings is, however, preferred.

Both, the IL-2 receptor  $\gamma$  chain molecule which is soluble in an aqueous solution (in the present invention this is defined to be the mature type of IL-2 receptor  $\gamma$  chain molecule which lacks the transmembrane and cytoplasmic regions, hereunder referred to as the "soluble IL-2 receptor  $\gamma$  chain molecule" and the gene which codes for the soluble IL-2 receptor  $\gamma$  chain molecule were prepared for the first time in the world.

In order to produce the soluble IL-2 receptor  $\gamma$  chain molecule, a cDNA is prepared which has a stop codon incorporated, near the 3'-end of the site which codes for the extracellular region of the IL-2 receptor  $\gamma$  chain, and it is inserted into an expression vector in the same manner as above, and expression may be conducted in an eucaryote such as a CHO cell or a mouse L929 cell or a procaryote such as E. coli. The host cell may be any of eucaryotes and procaryotes, however, the former being employed with advantages. According to the present invention, the gene encoding the soluble IL-2 receptor  $\gamma$  chain molecule was prepared by putting a stop codon, TAG, after the AAA which encodes the 230th Lys (see the base sequence listed as the Sequence Identification No. 6 in the Sequence Listings).

The amino acid sequence of the soluble IL-2 receptor  $\gamma$  chain molecule is shown as the sequence Identification No. 7 in the Sequence Listings. In addition, the amino acid sequence of the precursor with a signal peptide bound thereto is shown as the Sequence Identification No. 6 in the Sequence Listings.

For clarification only, the signal peptide is constituted from the -22nd Met to the -1st Gly of the precursor, while the sequence from the 1st Leu to the 230th Lys being for the desired molecule.

In order to produce the soluble IL-2 receptor  $\gamma$  chain molecule by use of an eucaryote such as CHO cells, mouse L929 cells or the like, a gene constructed by joining an appropriate stop codon to a gene encoding the amino acid sequence shown in Sequence Identification No. 6 in the Sequence Listings may be used.

The base sequence of the gene used may be arbitrary so far as it exactly corresponds to the amino acid sequence as shown as Sequence Identification No. 6 in the Sequence Listings.

Namely there is no need to limit the use of a cloned natural gene only. None the less, the use of the base sequence shown as Sequence Identification No. 6 in the Sequence Listings, namely the naturally occurring DNA sequence, is preferably used.

For the production of the soluble IL-2 receptor  $\gamma$  chain molecule which utilizes a procaryote such as E. coli,

a gene which encodes the amino acid sequence listed in the Sequence Identification No. 7 in the Sequence Listings should be inserted between the initiation codon ATG and an appropriate stop codon.

Of course it is not necessary that the base sequence of the gene which encodes the amino acid sequence shown as the Sequence Identification No. 7 in the Sequence Listings should be the natural one as shown in Sequence Identification No. 7 in the Sequence Listings.

But, the natural sequence shown in the Sequence Identification No. 7 in the Sequence Listings is recommended to be used.

By the way, the conditions for the culture medium and culturing when the host is cultured to produce the desired IL-2 receptor  $\gamma$  chain molecule or the soluble IL-2 receptor  $\gamma$  chain molecule may be conventional.

Concretely, L broth or the like may be used when the host is a procaryote such as *E. coli*, and the culturing conditions are usually 37 ° C for about 12-16 hours.

If the host is an eucaryote, for example, CHO cells, mouse L929 cells or the like, then Dulbecco's Modified Eagle Medium which contains 10% fetal bovine serum or the like, may be used. There is no need to be limited to any particular culturing conditions, but usually the culturing is carried out in the presence of 5% CO<sub>2</sub> at 37 ° C for 3-4 days.

Any conventional purification method may be employed for the purification of the thus harvested IL-2 receptor  $\gamma$  chain molecule or soluble IL-2 receptor  $\gamma$  chain molecule.

In an illustrative purification method, ion exchange chromatography, reverse phase chromatography, chromatofocusing, gel filtration, SDS electrophoresis, etc. may be used alone or in combination.

As mentioned above, there may be produced a recombinant human IL-2 receptor  $\gamma$  chain molecule which contains no substantial amount of the other human proteins. This recombinant human IL-2 receptor  $\gamma$  chain molecule which is substantially free of the other human proteins may be utilized as a medicine such as an immune response regulatory agent, as will be mentioned later.

According to the present invention, the human IL-2 receptor  $\gamma$  chain molecule is not limited to amino acid sequences shown in Sequence Identification Nos. 5 and 7 in the Sequence Listings, and includes all the polypeptides which possess the activity of the human IL-2 receptor  $\gamma$  chain molecule.

Therefore, (1) partially converted or (2) substituted versions or (3) one or more N- or C-terminal amino acid addition versions of the amino acid sequence shown in the Sequence Identification No. 5 or 7 in the Sequence Listings are included in the human IL-2 receptor  $\gamma$  chain molecule according to the present invention, so far as they substantially preserve the activity of the human IL-2 receptor  $\gamma$  chain molecule.

Further, as long as the activity of the human IL-2 receptor  $\gamma$  chain molecule is substantially maintained, those which received treatment of the polypeptide chain with polyethylene addition, acetylation or amidation are included in the human IL-2 receptor  $\gamma$  chain molecule of the present invention.

The method for the production of the human IL-2 receptor  $\gamma$  chain molecule is not limited to genetic recombination, and chemical synthesis such as solid phase method may also be utilized.

The IL-2 receptor  $\gamma$  chain molecule according to the present invention, particularly the human one, may be used as an immune response regulatory agent. That is, the present invention relates to an immune response regulatory agent which contains a therapeutically effective amount of an IL-2 receptor  $\gamma$  chain molecule.

The content of an IL-2 receptor  $\gamma$  chain molecule in an immune response regulatory agent which contains an IL-2 receptor  $\gamma$  chain molecule, is usually 0.1-100% by weight, preferably 0.5-70% by weight per 100% by weight of the immune response regulatory agent. If necessary, a stabilizing agent such as mannitol or a diluent may be added thereto.

The present immune response regulatory agent may be administered orally, but administration of injections via the parenteral route is desired. Needless to say, the agent intended for parenteral administration is desired to be prepared in a form suitable for such administration.

The dosage for human adults is usually 0.001-1000 mg, preferably 0.01-10 mg per day. Of course, the above dosage is only a standard, more or less dosage may be appropriately selected by depending on the condition of the disease, body weight, etc.

The diseases to which the immune response regulatory agent according to the present invention which contains an IL-2 receptor  $\gamma$  chain molecule may be applied, include rheumatoid arthritis, rejection at the time of organ transplantation, etc., without being limited thereto.

The cDNA for the present IL-2 receptor  $\gamma$  chain may be utilized also for detection and assay of a gene of an IL-2 receptor  $\gamma$  chain which is present in cells, tissues, etc.

Concretely, the present cDNA labelled with an isotope such as <sup>32</sup>P or biotin is used as a probe, and Southern blot technique (Journal of Molecular Biology, 98, p. 503, 1975) may be used for detection and assay of DNA, while Northern blot technique (Proceedings of the National Academy of Sciences USA, 77, p. 5201, 1980), etc. may be used in the case of RNA.



For the preparation of an antibody to the present IL-2 receptor  $\gamma$  chain, the IL-2 receptor  $\gamma$  chain molecule separated and purified according to the manner mentioned above may be used as the antigen. In case of the human IL-2 receptor  $\gamma$  chain molecule the antibody may be effectively obtained by using a cell for immunisation, which is from the same species but different from humans and which is transfected with the DNA for the present humans IL-2 receptor  $\gamma$  chain as the antigen. Particularly, the screening becomes easier when a monoclonal antibody is used.

Further, a peptide comprising the sequence shown as the Sequence Identification No. 8 in the Sequence Listings which corresponds to the N-terminal sequence of the human IL-2 receptor  $\gamma$  chain molecule may be synthesized, for example, with a peptide synthesizer, and may be combined with another carrier protein such as bovine serum albumin for use as the antigen. In addition, a sequence corresponding to a portion of the amino acid sequence shown as the Sequence Identification No. 5 or 7 in the Sequence Listings may be synthesized, and also its combination with a carrier protein may be used as the antigen. Of course, the antigen may be a polypeptide which comprises the amino acid sequence listed as the Sequence Identification No. 5 or 7 in the Sequence Listings.

The thus prepared anti-human IL-2 receptor  $\gamma$  chain antibody may be labelled with an isotope such as  $^{125}\text{I}$ , an enzyme or biotin and used for detection and assay of human receptor  $\gamma$  chain molecule present on the surface of cells or in the body fluid.

Here, the antibody may be polyclonal, but a monoclonal antibody is preferred.

Among the anti-human IL-2 receptor  $\gamma$  chain antibodies, those capable of inhibiting the binding between IL-2 receptor  $\beta$  and  $\gamma$  chains and preventing the transduction of signals from IL-2 may be used as medicines for diagnosis and treatment of diseases which are considered to advance due to excessive or disordered production of IL-2 and for prevention of rejection at the time of organ transplantation, etc. That is, the present invention also relates to an immune response regulatory agent which contains a therapeutically effective amount of an antibody which is able to bind to an IL-2 receptor  $\gamma$  molecule. The antibody may be polyclonal, but a monoclonal antibody is preferred.

The content of an anti-IL-2 receptor  $\gamma$  chain molecule antibody in an immune response regulatory agent which contains an antibody capable of binding to an IL-2 receptor  $\gamma$  chain molecule, is usually 0.1-100% by weight, and preferably 0.5-70% by weight per 100% by weight of the immune response regulatory agent. If necessary, a stabilizing agent such as mannitol or a diluent may be added thereto.

The present immune response regulatory agent may be administered orally, but administration of injections via a parenteral route is preferred. Needless to say, the agent intended for parenteral administration is preferably prepared in a form suitable for such administration.

The dosage for human adults is usually 0.001-1000 mg, preferably 0.01-10 mg per day. Of course, the above dosage is only a standard, a greater or lesser dosage may be appropriately selected depending on the condition of the disease, body weight, etc.

The immune response regulatory agent according to the present invention which contains an anti-IL-2 receptor  $\gamma$  chain molecule antibody may be applied to various diseases including rheumatoid arthritis, rejection at the time of organ transplantation, etc., without being limited thereto.

In order to obtain the IL-2 receptor  $\gamma$  chain cDNA, the polypeptide and antibodies against these polypeptides of other species the above described procedure may be used. Furthermore it is possible to utilize the human cDNA or an anti-human IL-2 receptor  $\gamma$  chain antibody obtained according to the above procedure for screening cDNA-libraries (or in case of using antibodies expression libraries) made of mRNA of different species. The methods employed in screening cDNA libraries/expression libraries are well known in the art and do not require a detailed illustration.

A more detailed explanation will be made hereunder regarding the present invention with reference to the drawings and examples.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the structure of Primers Nos. 1-6.

Fig. 2 is a drawing which shows the process for construction of expression vector pSRG1.

Fig. 3 shows a Scatchard plot which shows the state of IL-2 bound to the receptors on various cells.

Fig. 4 is a drawing which shows internalization of IL-2 by various cells

Fig. 5 illustrates the construction of expression vector pSD-G1.



**EXAMPLE 1: Separation and purification of IL-2 receptor  $\gamma$  chain molecules and determination of the N-terminal amino acid sequence**

To a pellet of  $4 \times 10^{10}$  MOLT  $\beta$  cells was added 800 ml of a RPMI1640 medium (manufactured by Gibco Inc.) which contains 30 nM of human recombinant IL-2 (manufactured by Ajinomoto Inc.) and 10% fetal bovine serum (manufactured by Hyclone Inc.), and then incubation was carried out at 37 °C for 1 hour. Next, the cells were subjected to centrifugation (220 g x 10 min.), a pellet was prepared and 800 ml of a buffer solution (0.14 M of NaCl, 0.5% NP-40, 2mM of PMSF, 1 mM of EDTA and 20 mM of Tris hydrochloride buffer solution containing 0.1% aprotinin, pH 7.5) was added for solubilization, followed by incubation at 4 °C for 1 hour for cytolysis.

Thereafter, the solubilized cell fraction was charged into a column packed with 1 ml of Affigel 10 (manufactured by Biorad Inc.) at 4 °C at a rate of about 50 ml/min, to which 10 mg of TU11 or a mouse monoclonal anti-IL-2 receptor  $\beta$  chain antibody (International Immunology, 1, p. 373, 1989) had been immobilized per 1 ml of gel beads.

The column was washed first with 300 ml of wash liquid A (0.14 M of NaCl, 1% NP-40, 2 mM of EDTA, 0.1% of SDS and 20 mM of Tris hydrochloride buffer solution containing 1% sodium deoxycholate, pH 7.5), then with 300 ml of wash liquid B (0.5 M of NaCl, 20 mM of Tris hydrochloride buffer solution containing 1% NP-40, pH 7.5), and finally with 50 ml of wash liquid C (20 mM of Tris hydrochloride buffer solution, pH 7.5).

2 ml of 8M urea was charged into the washed column to elute the IL-2/IL-2 receptor  $\beta$  chain/IL-2 receptor  $\gamma$  chain which had been bound to the column. The eluate was placed in a dialysis tube (manufactured by Sanko-Jun-Yaku Inc.), and was allowed to stand under reduced pressure for concentration to 0.4 ml, and this volume was divided into two portions of 0.39 ml and 0.01 ml, each subjected to dimensional polyacrylamide electrophoresis (isoelectric focusing for the first, and SDS electrophoresis for the second).

After electrophoresis, the proteins of the eluate (0.39 ml portion), were electrically transferred to an Imobilon P membrane (manufactured by Millipore Inc.). The gel used for electrophoresis of the 0.01 ml of the eluate was subjected to silver staining (manufactured by Dai-Ichi Kagaku Yakuhin Inc.), and the position of IL-2 receptor  $\gamma$  chain molecules after migration was confirmed.

The transfer site of the IL-2 receptor  $\gamma$  chain molecules was cut off from the Imobilon P membrane, and an amino acid sequencer 470A (manufactured by Applied Biosystem Inc.) was employed to determine the 20 N-terminal amino acid residues shown below. Here, the bracketed are possible candidates for which is lacking decisive evidence, and X shows a sequence which could not be identified.

(Leu, Ile)-(Asn, Cys)-(Thr, Phe)-Thr, Phe-Ile-Leu-Thr-Pro-Asn-Gly-Asn-Glu-(Asp, Arg)-(Thr, Ala)-X-Ala-(Asp, Gly)-Phe-Phe-Leu

**EXAMPLE 2: Isolation of a cDNA for a IL-2 receptor  $\gamma$  chain**

The entire RNA was separated from  $5 \times 10^6$  MOLT  $\beta$  cells with an RNA extraction kit (manufactured by Pharmacia Inc.). Then a mRNA purification kit (manufactured by Pharmacia Inc.) was used to purify the mRNA. cDNA was synthesized from the purified mRNA, using oligo dT as the primer, and using reverse transcriptase (manufactured by Takara Brewing Inc.).

In view of the N-terminal amino acid sequence of the IL-2 receptor  $\gamma$  chain molecules obtained in Example 1, 6 kinds of oligonucleotides as shown in Fig. 1 (corres. to Primer Nos. 1-6 in Fig. 1) were designed and synthesized with a DNA synthesizer 380A (manufactured by Applied Biosystem Inc.).

These oligonucleotides were used as the primers for synthesis of the cDNA which was in turn subjected to PCR with Taq polymerase (manufactured by Takara Brewing Inc.) (strand separation at 94 °C, annealing at 50 °C, strand elongation at 72 °C, 30 cycles), using a thermal cycler (manufactured by Perkin Elmer Cetus Inc.).

cDNA amplified by PCR was purified with a MERMAID kit (manufactured by Bio-101 Inc.). cDNA amplified by PCR was purified and labelled with  $^{32}$ P with a random primer labelling kit (manufactured by Takara Brewing Inc.). This was used as a probe for screening a cDNA library prepared in advance from MOLT  $\beta$  cells using random hexamer as the primer and  $\lambda$  ZAPII as the vector (manufactured by Stratagene Inc.). As a result, a cDNA clone (pIL-2R $\gamma$ 1) was obtained, and its base sequence was determined with a 7-DEAZA sequencing kit (manufactured by Takara Brewing Inc.). This sequence is shown as Sequence Identification

No. 1 in the Sequence Listings.

The present pIL-2R $\gamma$ 1 was a 3'-end deletion version, so additionally  $^{32}$ -P-labelled pIL-2R $\gamma$ 1 was used as a probe to obtain 3 cDNA clones with complete 3'ends (pIL-2R $\gamma$ 2, pIL-2R $\gamma$ 3 and pIL-2R $\gamma$ 4) from a cDNA library which had been prepared in the same manner as the above using oligo dT as the primer, and their

base sequences were determined in the same manner (Sequence Identification No. 2 in the Sequence Listings).

In this connection, pIL-R $\gamma$ 2, pIL-2R $\gamma$ 3 and pIL-2R $\gamma$ 4 all had the same base sequence, so the sequence of only pIL-2R $\gamma$ 2 with the longest 5'-end sequence is listed as Sequence Identification No. 2 in the Sequence Listings.

The entire base sequence of the IL-2 receptor  $\gamma$  chain molecule was determined in consideration of the thus clarified sequences of pIL-2R $\gamma$ 1 and pIL-2 $\gamma$ 2 in combination.

The sequence of cDNA for IL-2 receptor  $\gamma$  chain molecule is listed as Sequence Identification No. 3 in the Sequence Listings. In addition, the amino acid sequence which was presumed based on the base sequence is listed as Sequence Identification No. 3 in the Sequence Listings.

As a result, it was revealed that the present IL-2 receptor  $\gamma$  chain molecule comprises an open reading frame of 369 amino acids, 22 of which being for the signal sequence, and the sequence of the mature type of the protein consists of 347 amino acids.

That is, in the sequence listed as Sequence Identification No. 3 in the Sequence Listings, the signal peptide corresponds to the section from Met at the -22nd position to Gly at the -1st position. The sequence from ATG corresponding to Met at the -22nd position to GGG which corresponds to Gly at the -1st position is the gene which encodes the signal peptide.

The mature type of polypeptide corresponds to the section from Leu at the 1st position to Thr at the 347th position. The gene which encodes the mature type of the polypeptide is the sequence from CTG corresponding to Leu at the 1st position to ACC which corresponds to Thr at the 347th position in Sequence Identification No. 3 in the Sequence Listings. Incidentally, *E. Coli* which had been transformed with the vector including the cDNA for the IL-2 receptor  $\gamma$  chain molecule, i.e. the sequence listed as Sequence Identification No. 3 in the Sequence Listings, has been deposited with the Fermentation Research Institute, Agency of Industrial Science and Technology (Deposit No.: AJ12706, FERM BP-4200).

Further it was revealed that the extracellular region, the transmembrane region and the intracellular region of the IL-2 receptor  $\gamma$  chain molecule comprise 232, 29 and 86 amino acids, respectively. In other words, in the mature type of the polypeptide described in Sequence Identification No. 3 in the Sequence Listings, the section from the 1st Leu to the 232nd Asn is the extracellular region, the one from the 233rd Pro to the 261st Leu is the transmembrane region, and the one from the 262nd Glu to the 347th Thr is the intracellular region.

#### EXAMPLE 3: Binding of IL-2 to cells transfected with an IL-2 receptor $\gamma$ chain cDNA

cDNA clone pIL-2R $\gamma$ 1 obtained in Example 2 was cut with restriction enzymes XbaI and NcoI (both manufactured by Takara Brewing Inc.) to prepare a cDNA fragment with 0.9 kb in length, while a cDNA fragment of 0.7 kb was prepared by cutting pIL-2R $\gamma$ 2 with the same restriction enzymes XbaI and NcoI. The two fragments were cut with XbaI, after which each was mixed with the vector pcDSR $\alpha$  the terminal of which had been dephosphorylated with alkaline phosphatase (Takara Brewing Inc.) (Molecular Cellular Biology, 8, p. 466, 1988), and ligation was carried out with T4DNA ligase (Takara Brewing Inc.), thus constructing expression vector pSRG1 (Fig. 2).

The expression vectors pSRA4 having the cDNA for the IL-2 receptor  $\alpha$  chain incorporated therein, and pSRB5 having the cDNA for the IL-2 receptor  $\beta$  chain incorporated therein were also constructed in the same manner.

Together with a neomycin-resistance gene, pSRB5 was transfected alone into mouse L929 cells (50  $\mu$ g/l x 10<sup>7</sup>, 1500 V, 25  $\mu$ F) using a gene pulser (manufactured by Biorad Inc.), and the same transfection was also conducted using pSRA4 and pSRB5 simultaneously, pSRB5 and pSRG1 simultaneously, and pSRA4, pSRB5 and pSRG1 simultaneously. The cells were cultured for 3 weeks, using Dulbecco's Modified Eagle Medium (manufactured by Gibco Inc.) which contained 1 mg/ml of neomycin and 10% fetal bovine serum, and the cells with the object genes incorporated therein were cloned by limiting dilution, thus harvesting L $\beta$ -1 cells (L929 cells with IL-2 receptor  $\beta$  chain expression), L $\beta$  $\gamma$ -9 cells (L929 cells with IL-2 receptor  $\beta$  and  $\gamma$  chain expression), L $\alpha$  $\beta$ -2 cells (L929 cells with IL-2 receptor  $\alpha$  and  $\beta$  chain expression), L $\alpha$  $\beta$  $\gamma$ -4 cells (L929 with IL-2 receptor  $\alpha$ ,  $\beta$  and  $\gamma$  chain expression).

In the presence or absence of 3  $\mu$ M of unlabelled IL-2 various concentrations of IL-2 labelled with <sup>125</sup>I (4 x 10<sup>6</sup> dpm/pmole) by the chloramine-T method were added to 2 x 10<sup>6</sup> L $\beta$ -1 cells, L $\beta$  $\gamma$ -9 cells, L $\alpha$  $\beta$ -2 cells and L $\alpha$  $\beta$  $\gamma$ -4 cells, respectively, and a reaction was carried out at 4°C for 1.5 hours. The radioactivity of <sup>125</sup>I-IL-2 bound or not bound to the cells was determined. The value for the background or the binding radioactivity in the case of addition of unlabelled IL-2 was subtracted from each of the measurements to calculate the binding amounts, the binding ability and the binding affinity of IL-2 to the receptor as

determined by a Scatchard plot.

Fig. 3 shows the results of the Scatchard plot, while Table 1 lists the binding affinity calculated from the gradient of the graph of the Scatchard plot. IL-2 binding was not observed for L $\beta$ -1 cells or mouse L929 cells expressing (non-lymphoid cells) only human IL-2 receptor  $\beta$  chain, whereas the binding affinity of IL-2 was found to be 4.6 nM, representing an intermediate affinity value for L $\beta$  $\gamma$ -9 cells with both  $\beta$  and  $\gamma$  chain expression, in the same manner as in the case of lymphoid cells. Further, for L $\alpha$  $\beta$ -2 cells with IL-2 receptor  $\alpha$  and  $\beta$  chain expression, the binding affinity was a pseudo high affinity of 600 pM. For L $\alpha$  $\beta$  $\gamma$ -4 cells with  $\gamma$  chain expression as well as  $\alpha$  and  $\beta$  chain expression, the binding was a biphasic one, of which the high affinity binding was 77 pM, almost equal to that of lymphoid cells. Surely it was proven that the isolated cDNA is the cDNA encoding the IL-2 receptor  $\gamma$  chain molecule present in human lymphoid cells.

TABLE 1

Name of cells	Binding affinity
L $\beta$ -1	-
L $\beta$ $\gamma$ -9	4.6 nM
L $\alpha$ $\beta$ -2	600 pM
L $\alpha$ $\beta$ $\gamma$ -4	77 pM (high affinity binding) 2.4 nM (low affinity binding)

#### EXAMPLE 4: Internalization of IL-2 by cells transfected with the IL-2 receptor $\gamma$ chain cDNA

Ten nM of  $^{125}$ I-IL-2 was added to  $2 \times 10^6$  L $\beta$  $\gamma$ -9 cells, L $\alpha$  $\beta$ -2 cells, L $\alpha$  $\beta$  $\gamma$ -4 cells, respectively, and the mixture was then reacted at 0°C for 1 hour, followed by washing with 10 mM of phosphate buffer solution containing 0.15 M of NaCl, at pH 7.5 (PBS), to remove  $^{125}$ I-IL-2 not bound to the cells.

Next the cell suspension was incubated at 37°C sequentially, immediately after which the cells were suspended in cooled 0.2 M glycine hydrochloride buffer solution (pH 2.8), and the suspension was allowed to stand for 10 minutes. The amount of the  $^{125}$ I-IL-2 scaled off into the solution was determined to be that of the  $^{125}$ I-IL-2 which had been bound to the receptor on the cell membrane, while that of the  $^{125}$ I-IL-2 left in the cells was deemed to be that of the  $^{125}$ I-IL-2 in the cells.

As a result, as shown in Fig. 4, the internalization of IL-2 did not occur even with lapse of time, but it was made clear that the IL-2 internalization occurs for L $\beta$  $\gamma$ -9 cells and L $\alpha$  $\beta$  $\gamma$ -4 cells as time goes by.

In other words this result evidences that the presence of the IL-2 receptor  $\gamma$  chain molecule contributes to the internalization of IL-2, the present molecule is involved in transduction of signals from IL-2, and it is thus a molecule indispensable for the functions of IL-2.

#### Example 5: Preparation of antibodies to the N-terminal peptide of IL-2 receptor $\gamma$ chain molecule and IL-2 receptor $\gamma$ chain molecule

A peptide corresponding to the N-terminal sequence of the IL-2 receptor  $\gamma$  chain listed as Sequence Identification No. 8 in the Sequence Listings, was synthesized with a peptide synthesizer (Applied Biosystem Inc.). 5 mg of the synthesized peptide was bound to 10 mg of KLH (keyhole limpet hemocyanin manufactured by Wako-Jun-Yaku Inc.) using m-male-imidobenzoyl-N-hydroxysuccinimide ester (Pierce Inc.), and then mixed with Freund's complete adjuvant (manufactured by Difco Inc.) at a proportion of 1:1 to prepare an emulsion, a sixth of which was used for immunization of each rabbit, and a twelfth of which was used for that of each mouse, both by intramuscular injection.

The same operation was repeated twice 2 weeks apart, and for the preparation of a rabbit polyclonal antibody, the blood was taken 7 days after the final immunization, after which the serum was separated. This serum was further subjected to salting out with 40% saturation ammonium sulfate. An IgG fraction was obtained by affinity chromatography using protein A sepharose (manufactured by Pharmacia Inc.). Fifty milliliters of the serum provided 270 mg of the IgG fraction. Next, in order to prepare a mouse monoclonal antibody, 3 days after the final immunization, mouse spleen cells and myeloma cells (P3X63Ag8.653) were mixed at a portion of 10:1 to induce their fusion in the presence of polyethylene glycol #4000 (manufactured by Flow Inc.), and selection of the fused cells was carried out in RPMI1640 medium which contained a HAT solution (manufactured by Flow Inc.) and 10% fetal bovine serum. The supernatant from the culture of the fused cells was subjected to a reaction in a flexible 96-well flat plate (manufactured by Falcon Inc.) with 10

$\mu\text{g/ml}$  of peptide coated thereon, washed with 10 mM phosphate buffer solution (pH 7.5) containing 0.05% Tween 20 and 0.15M of NaCl, and then reacted with  $^{125}\text{I}$ -labelled anti-mouse immunoglobulin antibody (manufactured by Amersham Inc.) and washing in the same manner. Selection of mouse monoclonal antibody-producing hybridomas for the peptide is made by measuring the radioactivity bound to each well.

Balb/c mice which had been intraperitoneally injected 1 week before with 0.5 ml/mouse of Pristan (manufactured by Wako-Jun-Yaku Inc.) were further injected intraperitoneally with  $1 \times 10^7$  hybridomas per mouse, followed by collection of ascites after 7-10 days. The ascites were subjected to salting out with 40% saturation ammonium sulfate, and an antibody was harvested by affinity chromatography using protein A sepharose. Thirty five grams of the antibody was recovered from 10 ml of the ascites.

For the preparation of an antibody against the IL-2 receptor  $\gamma$  chain molecule, according to the method as shown in Example 3, the cDNA for the IL-2 receptor  $\gamma$  chain was introduced into Balb/3T3 cells, and immunization was accomplished by intraperitoneal injection of cells with IL-2 receptor  $\gamma$  chain molecule expressed thereon at a proportion of  $1 \times 10^7$  cells per Balb/c mouse.

The same procedures were repeated twice each 2 weeks, for the preparation of a polyclonal antibody, the blood was taken 7 days thereafter, followed by separation of the serum. The obtained serum was then subjected to salting out with 40% saturation ammonium sulfate. After that the IgG fraction was harvested by affinity chromatography using protein A sepharose.

For the preparation of a monoclonal antibody, fused cells are harvested in the same manner as above, 3 days after the final immunization. The supernatant from the culture was reacted with MOLT4 cells, washed with RPMI1640 medium containing 10% fetal bovine serum, followed by reaction with  $^{125}\text{I}$ -labelled anti-mouse immunoglobulin antibody (manufactured by Amersham Inc.) and washing in the same manner. Selection of mouse monoclonal antibody-producing hybridomas for the IL-2 receptor  $\gamma$  chain molecule is made by measuring of the radioactivity bound to the cells. An antibody was harvested in the same manner as the above. Four milligrams of polyclonal antibodies were recovered from 1 ml of the serum, while 23-38 g of a monoclonal antibody was recovered per 10 ml of the ascites.

#### Example 6: Preparation of a soluble IL-2 receptor $\gamma$ chain

For the preparation of the IL-2 receptor  $\gamma$  chain cDNA with a stop codon at the 3'-terminus in the extracellular region, PCR with Taq polymerase (strand separation at  $94^\circ\text{C}$ , annealing at  $50^\circ\text{C}$ , strand elongation at  $72^\circ\text{C}$ , 20 cycles) was conducted, by using as primers, oligomer 5'-AGCTCGAGCGCCATGTTGAAGCCCAT-3' and 5'-AACTCGAGAGGATTCTATTTTGAAGTAT-3' Including an XhoI site, which were synthesized with a DNA synthesizer 380A, and by using a thermal cycler, wherein pSRG1 prepared in Example 3 was used as the sample.

About 0.8 kb of the amplified band was recovered, then cut with XhoI (manufactured by Takara Brewing Inc.), after which ligation was carried out along with pSD(X) vector which had been cut with XhoI and dephosphorylated with alkaline phosphatase at the termini (Proceedings of the National Academy of Sciences USA, 85, p. 2434, 1988). The insertion in the positive direction was selected for construction of pSD-G1. Fig. 5 shows the construction of the expression vector pSD-G1.

The aforementioned operation thus enabled preparation of the sequence with the stop codon TAG inserted after the codon AAA which codes for the 230th Lys, as shown in Sequence Identification No. 6 in the Sequence Listings.

In a 6 cm dish (manufactured by Falcon Inc.)  $1.5 \times 10^5$  CHO cells (DHFR<sup>-</sup> strain) in the logarithmic phase were scattered, and cultured in  $\alpha\text{MEM}$  (Gibco Inc.) which contains 10% FCS, 2 mg/ml of  $\text{NaHCO}_3$  and 100  $\mu\text{g/ml}$  of kanamycin sulfate (Meiji Seika Inc.), at  $37^\circ\text{C}$  for 24 hours. Plasmid pSD-G1 is transduced by the potassium phosphate method (Molecular Cloning, 2nd edition, 1989).

Thereafter, culturing is performed overnight. Then, the medium was replaced by a fresh one for further culturing for 24 hours, after which the cells were divided, and cultured for an additional 24 hour. Next, the medium was replaced by a fresh one of the same composition but lacking nucleic acid, and culturing was effected for 7-10 days for selection of DHFR<sup>+</sup> cells.

The supernatant from the culture was reacted in a 96-well flexible plate with a coating of 10  $\mu\text{g/ml}$  of the monoclonal antibody prepared in Example 5, and washed with 10 mM phosphate buffer solution (pH 7.5) containing 0.05% Tween 20 and 0.15M of NaCl, and followed by addition of a monoclonal antibody labelled with  $^{125}\text{I}$  by the chrolamine-T method (an antibody other than that used for the coating) and washed in the same manner. The selection of cells with soluble IL-2 receptor  $\gamma$  chain expression was performed by measurement of the radioactivity bound to each cell.

Fifteen liters of the supernatant from the culture of the strain with high expression of the soluble IL-2 receptor  $\gamma$  chain molecule is concentrated to 1,500 ml, and added to 5 ml of Sepharose 4B (5 mg/ml,

manufactured by Pharmacia Inc.) with the anti-IL-2 receptor  $\gamma$  chain antibody prepared in Example 5 bound thereto. The column is washed with 100 ml of PBS, and the bound soluble IL-2 receptor  $\gamma$  chain molecule was eluted with 0.1 M of acetic acid (pH 3.1), immediately after which the eluate was neutralized with 1M Tris-HCl buffer solution (pH 7.5), and dialyzed against 50 mM of Tris-HCl buffer solution (pH 8.0) which contains 0.1 M of NaCl, for elution of the soluble IL-2 receptor  $\gamma$  chain molecule. The foregoing operation concentrates the soluble IL-2 receptor  $\gamma$  chain molecule to about 10,000 times, and provides a recovery rate of about 70%.

This elution fraction is purified to a high level by reverse phase HPLC using an ODS column (Yamamura Kagaku Inc.). Ten milliliters of the elution fraction is placed in an ODS column equilibrated with 0.1% trifluoroacetic acid (pH 2.0, manufactured by Nakaraitesugue Inc.), and the adsorbed proteins were eluted according to a linear concentration gradient with 0-80% acetonitrile which contains 0.1% trifluoroacetic acid, for separation and purification of the soluble IL-2 receptor  $\gamma$  chain molecule. The present operation concentrates the soluble IL-2 receptor  $\gamma$  chain molecule about 25,000-fold and produces a final recovery rate of 45%.

Analysis with an amino acid analyzer showed that the amino acid sequence of the recovered soluble IL-2 receptor  $\gamma$  chain molecule is the same one listed as Sequence Identification No. 7 in the Sequence Listings.

The IL-2 receptor  $\gamma$  chain molecule and the soluble IL-2 receptor  $\gamma$  chain molecule according to the present invention is a substance which has a wide variety of uses, for example for clarification of the IL-2/IL-2 receptor system or as an immune response regulatory agent, etc.

Moreover, a gene encoding IL-2 receptor  $\gamma$  chain molecule and a gene encoding a soluble IL-2 receptor  $\gamma$  chain molecule are substances which may produce useful IL-2 receptor  $\gamma$  chain molecules and soluble IL-2 receptor  $\gamma$  chain molecules by application of genetic engineering. Furthermore, an antibody to IL-2 receptor  $\gamma$  molecule is also a useful substance, which may be utilized as an immune response regulatory agent, etc.

SEQUENCE LISTINGS

## GENERAL INFORMATION

## Applicant:

Name: Ajinomoto Co. Inc.  
 Street: 15-1, Kyobashi 1 Chome  
 City: Chuo-Ku Tokyo 104  
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TITLE OF THE INVENTION: IL-2 RECEPTOR  $\gamma$ -CHAIN MOLECULE

NUMBER OF SEQUENCES: 16

## COMPUTER READABLE FORM

Computer: IBM-compatible  
 Operating system: MS-DOS 5.0  
 Software: Microsoft-Word

## PRIOR APPLICATION DATA:

Filing date: April 23, 1992  
 Classification: class 12

## INFORMATION FOR SEQ.ID.NO. 1

## Sequence characteristics

Length: 1062 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

## Original source

Organism: Homo sapiens  
 Cell type: Lymphocyte

## Sequence description

SEQ.ID.NO.: 1

GAAGAGCAAG	CGCCATGTTG	AAGCCATCAT	TACCATTAC	ATCCCTCTTA	TTCCTGCAGC	60
TGCCCCCTGCT	GGGAGTGGGG	CTGAACACGA	CAATTCTGAC	GCCCAATGGG	AATGAAGACA	120
CCACAGCTGA	TTTCTTCCTG	ACCACTATGC	CCACTGACTC	CCTCAGCGTT	TCCACTCTGC	180
CCCTCCCAGA	GGTTCAGTGT	TTTGTGTTCA	ATGTCGAGTA	CATGAATTGC	ACTTGGAACA	240
GCAGCTCTGA	GCCCCAGCCT	ACCAACCTCA	CTCTGCATTA	TTGGTACAAG	AACTCGGATA	300
ATGATAAAGT	CCAGAAGTGC	AGCCACTATC	TATTCTCTGA	AGAAATCACT	TCTGGCTGTC	360
AGTTGCAAAA	AAAGGAGATC	CACCTCTACC	AAACATTTGT	TGTTTCAGCTC	CAGGACCCAC	420
GGGAACCCAG	GAGACAGGCC	ACACAGATGC	TAAAACCTGCA	GAATCTGGTG	ATCCCCTGGG	480
CTCCAGAGAA	CCTAACACTT	CACAACTGA	GTGAATCCCA	GCTAGAACTG	AACTGGAACA	540
ACAGATTCTT	GAACCACTGT	TTGGAGCACT	TGGTGCAGTA	CCGGACTGAC	TGGGACCACA	600
GCTGGACTGA	ACAATCAGTG	GATTATAGAC	ATAAGTTCTC	CTTGCTAGT	GTGGATGGGC	660
AGAAACGCTA	CACGTTTCGT	GTCGGAGGCC	GCTTTAACCC	ACTCTGTGGA	AGTGCTCAGC	720

```

ATTGGAGTGA ATGGAGCCAC CCAATCCACT GGGGGAGCAA TACTTCAAAA GAGAATCCTT 780
TCCTGTTTGC ATTGGAAGCC GTGGTTATCT CTGTTGGCTC CATGGGATTG ATTATCAGCC 840
TTCTCTGTGT GTATTCTCTGG CTGGAACGGA CGATGCCCCG AATTCCCACC CTGAAGAACC 900
TAGAGGATCT TGTTACTGAA TACCACGGGA ACTTTTCGGC CTGGAGTGGT GTGTCTAAGG 960
GACTGGCTGA GAGTCTGCAG CCAGACTACA GTGAACGACT CTGCCTCGTC AGTGAGATTC 1020
CCCCAAAAGG AGGGGGCCCTT GGGGAGGGGC CTGGGGCCTC CC 1062

```

# INFORMATION FOR SEQ.ID.NO. 2

## Sequence characteristics

```

Length:      1393 base pairs
Type:        nucleic acid
Strandedness: single
Topology:    linear

```

Molecule type: DNA (cDNA)

## Original source

```

Organism:    Homo sapiens
Cell type:    Lymphocyte

```

## Sequence description

SEQ.ID.NO.: 2

```

GGGCTGAACA CGACAATTCT GACGCCCAAT GGAATGAAG ACACCACAGC TGATTTCTTC 60
CTGACCACTA TGCCCACTGA CTCCCTCAGC GTTTCCTACTC TGCCCTCCC AGAGGTTCCAG 120
TGTTTTGTGT TCAATGTGCA GTACATGAAT TGCACTTGGA ACAGCAGCTC TGAGCCCCAG 180
CCTACCAACC TCACTCTGCA TTATTGGTAC AAGAACTCGG ATAATGATAA AGTCCAGAAG 240
TGCAGCCACT ATCTATTCTC TGAAGAAATC ACTTCTGGCT GTCAGTTGCA AAAAAAGGAG 300
ATCCACCTCT ACCAAACATT TGTTGTTTCTG CTCCAGGACC CACGGGAACC CAGGAGACAG 360
GCCACACAGA TGCTAAAACT GCAGAATCTG GTGATCCCTT GGGCTCCAGA GAACCTAACA 420
CTTCACAAAC TGAGTGAATC CCAGCTAGAA CTGAACTGGA ACAACAGATT CTTGAACCAC 480
TGTTTGAGGC ACTTGGTGCA GTACCGGACT GACTGGGACC ACAGCTGGAC TGAACAATCA 540
GTGGATTATA GACATAAGTT CTCCTTGCCT AGTGTGGATG GGCAGAAACG CTACACGTTT 600
CGTGTTCTGA GCCGCTTTAA CCCACTCTGT GGAAGTGCTC AGCATTGGAG TGAATGGAGC 660
CACCCAATCC ACTGGGGGAG CAATACTTCA AAAGAGAATC CTTTCCTGTT TGCATTGGAA 720
GCCGTGGTTA TCTCTGTTGG CTCCATGGGA TTGATTATCA GCCTTCTCTG TGTGTATTTC 780
TGGCTGGAAC GGACGATGCC CCGAATTCCC ACCCTGAAGA ACCTAGAGGA TCTTGTACT 840
GAATACCACG GGAACCTTTC GGCCTGGAGT GGTGTGTCTA AGGGACTGGC TGAGAGTCTG 900
CAGCCAGACT ACAGTGAACG ACTCTGCCTC GTCAGTGAGA TTCCCCCAA AGGAGGGGCC 960
CTTGGGGGAG GGCCTGGGGC CTCCCCATGC AACCAGCATA GCCCCCTACTG GGCCCCCCCCA 1020
TGTTACACCC TAAAGCCTGA AACCTGAACC CCAATCCTCT GACAGAAGAA CCCCAGGGTC 1080
CTGTAGCCCT AAGTGGTACT AACTTTCCTT CATTCAACCC ACCTGCGTCT CATACTCACC 1140
TCACCCCACT GTGGCTGATT TGGAAATTTG TGCCCCCATG TAAGCACCCC TTCATTGGC 1200
ATTCCCCACT TGAGAATTAC CCTTTTGCCC CGAACATGTT TTTCTTCTCC CTCAGTCTGG 1260
CCCTTCCTTT TCGCAGGATT CTTCCTCCCT CCCTCTTTC CTCCCTTCCT CTTTCCATCT 1320
ACCTCCGAT TGTTCTTGAA CCGATGAGAA ATAAAGTTTC TGTTGATAAT CATCAAAAAA 1380
AAAAA AAA

```

1393



## INFORMATION FOR SEQ.ID.NO. 3

## Sequence characteristics

Length: 1470 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

## Feature

Key: CDS  
 Location: 15..1124

## Feature

Key: sig\_peptide  
 Location: 15..80

## Feature

Key: mat\_peptide  
 Location: 81..1124

## Sequence description

SEQ.ID.NO.: 3

25	GAAGAGCAAG CGCC ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA	50
	Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu	
	-20 -15	
	TTC CTG CAG CTG CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG	98
	Phe Leu Gln Leu Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu	
	-10 -5 1 5	
30	ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT	146
	Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr	
	10 15 20	
	ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT	194
	Met Pro Thr Asp Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val	
	25 30 35	
35	CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC	242
	Gln Cys Phe Val Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser	
	40 45 50	
	AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG	290
	Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys	
	55 60 65 70	
	AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT	338
40	Asn Ser Asp Asn Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser	
	75 80 85	
	GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC	386
	Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu	
	90 95 100	
	TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA	434
45	Tyr Gln Thr Phe Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg	
	105 110 115	
	CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT	482
	Gln Ala Thr Gln Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala	
	120 125 130	
	CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG	530
50	Pro Glu Asn Leu Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu	
	135 140 145 150	

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	AAC	TGG	AAC	AAC	AGA	TTC	TTG	AAC	CAC	TGT	TTG	GAG	CAC	TTG	GTG	CAG	578
	Asn	Trp	Asn	Asn	Arg	Phe	Leu	Asn	His	Cys	Leu	Glu	His	Leu	Val	Gln	
					155					160						165	
5	TAC	CGG	ACT	GAC	TGG	GAC	CAC	AGC	TGG	ACT	GAA	CAA	TCA	GTG	GAT	TAT	626
	Tyr	Arg	Thr	Asp	Trp	Asp	His	Ser	Trp	Thr	Glu	Gln	Ser	Val	Asp	Tyr	
				170					175							180	
	AGA	CAT	AAG	TTC	TCC	TTG	CCT	AGT	GTG	GAT	GGG	CAG	AAA	CGC	TAC	ACG	674
	Arg	His	Lys	Phe	Ser	Leu	Pro	Ser	Val	Asp	Gly	Gln	Lys	Arg	Tyr	Thr	
			185					190					195				
10	TTT	CGT	GTT	CGG	AGC	CGC	TTT	AAC	CCA	CTC	TGT	GGA	AGT	GCT	CAG	CAT	722
	Phe	Arg	Val	Arg	Ser	Arg	Phe	Asn	Pro	Leu	Cys	Gly	Ser	Ala	Gln	His	
		200					205					210					
	TGG	AGT	GAA	TGG	AGC	CAC	CCA	ATC	CAC	TGG	GGG	AGC	AAT	ACT	TCA	AAA	770
	Trp	Ser	Glu	Trp	Ser	His	Pro	Ile	His	Trp	Gly	Ser	Asn	Thr	Ser	Lys	
		215				220					225					230	
15	GAG	AAT	CCT	TTC	CTG	TTT	GCA	TTG	GAA	GCC	GTG	GTT	ATC	TCT	GTT	GGC	818
	Glu	Asn	Pro	Phe	Leu	Phe	Ala	Leu	Glu	Ala	Val	Val	Ile	Ser	Val	Gly	
				235						240						245	
	TCC	ATG	GGA	TTG	ATT	ATC	AGC	CTT	CTC	TGT	GTG	TAT	TTC	TGG	CTG	GAA	866
	Ser	Met	Gly	Leu	Ile	Ile	Ser	Leu	Leu	Cys	Val	Tyr	Phe	Trp	Leu	Glu	
				250					255					260			
20	CGG	ACG	ATG	CCC	CGA	ATT	CCC	ACC	CTG	AAG	AAC	CTA	GAG	GAT	CTT	GTT	914
	Arg	Thr	Met	Pro	Arg	Ile	Pro	Thr	Leu	Lys	Asn	Leu	Glu	Asp	Leu	Val	
			265				270						275				
	ACT	GAA	TAC	CAC	GGG	AAC	TTT	TCG	GCC	TGG	AGT	GGT	GTG	TCT	AAG	GGA	962
	Thr	Glu	Tyr	His	Gly	Asn	Phe	Ser	Ala	Trp	Ser	Gly	Val	Ser	Lys	Gly	
		280				285					290						
25	CTG	GCT	GAG	AGT	CTG	CAG	CCA	GAC	TAC	AGT	GAA	CGA	CTC	TGC	CTC	GTC	1010
	Leu	Ala	Glu	Ser	Leu	Gln	Pro	Asp	Tyr	Ser	Glu	Arg	Leu	Cys	Leu	Val	
					300						305					310	
	AGT	GAG	ATT	CCC	CCA	AAA	GGA	GGG	GCC	CTT	GGG	GAG	GGG	CCT	GGG	GCC	1058
	Ser	Glu	Ile	Pro	Pro	Lys	Gly	Gly	Ala	Leu	Gly	Glu	Gly	Pro	Gly	Ala	
				315						320					325		
30	TCC	CCA	TGC	AAC	CAG	CAT	AGC	CCC	TAC	TGG	GCC	CCC	CCA	TGT	TAC	ACC	1106
	Ser	Pro	Cys	Asn	Gln	His	Ser	Pro	Tyr	Trp	Ala	Pro	Pro	Cys	Tyr	Thr	
				330				335					340				
	CTA	AAG	CCT	GAA	ACC	TGAACCCCAA	TCCTCTGACA	GAAGAACCCC	AGGGTCCTGT								1161
	Leu	Lys	Pro	Glu	Thr												
35			345														
	AGCCCTAAGT	GGTACTAACT	TTCCTTCATT	CAACCCACCT	GCGTCTCATA	CTCACCTCAC											1221
	CCCACTGTGG	CTGATTTGGA	ATTTTGTGCC	CCCATGTAA	CACCCCTTCA	TTTGGCATTC											1281
	CCCACTTGAG	AATTACCCTT	TTGCCCGGAA	CATGTTTTTC	TTCTCCCTCA	GTCTGGCCCT											1341
	TCCTTTTCGC	AGGATTCTTC	CTCCCTCCCT	CTTTCCCTCC	CTTCCTCTTT	CCATCTACCC											1401
40	TCCGATTGTT	CCTGAACCGA	TGAGAAATAA	AGTTTCTGTT	GATAATCATC	AAAAAAAAAA											1461
	AAAAAAAAAA																1470

45

50

55

## INFORMATION FOR SEQ.ID.NO. 4

## Sequence characteristics

Length: 1110 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

## Feature

Key: CDS  
 Location: 1..1110

## Feature

Key: sig\_peptide  
 Location: 1..66

## Feature

Key: mat\_peptide  
 Location: 67..1110

## Sequence description

SEQ.ID.NO.: 4

25	ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG	48
	Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu	
	-20 -15 -10	
	CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG	96
	Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly	
	-5 1 5 10	
	AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC	144
	Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp	
30	15 20 25	
	TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG	192
	Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val	
	30 35 40	
	TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC	240
	Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro	
35	45 50 55	
	CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT	288
	Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn	
	60 65 70	
	GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT	336
	Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr	
40	75 80 85 90	
	TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT	384
	Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe	
	95 100 105	
	GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG	432
	Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln	
	110 115 120	
45	ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA	480
	Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu	
	125 130 135	
	ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC	528
	Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn	
	140 145 150	
50	AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC	576
	Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln Tyr Arg Thr Asp	
	155 160 165 170	

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	TGG	GAC	CAC	AGC	TGG	ACT	GAA	CAA	TCA	GTG	GAT	TAT	AGA	CAT	AAG	TTC	624
	Trp	Asp	His	Ser	Trp	Thr	Glu	Gln	Ser	Val	Asp	Tyr	Arg	His	Lys	Phe	
				175						180					185		
5	TCC	TTG	CCT	AGT	GTG	GAT	GGG	CAG	AAA	CGC	TAC	ACG	TTT	CGT	GTT	CGG	672
	Ser	Leu	Pro	Ser	Val	Asp	Gly	Gln	Lys	Arg	Tyr	Thr	Phe	Arg	Val	Arg	
			190						195					200			
	AGC	CGC	TTT	AAC	CCA	CTC	TGT	GGA	AGT	GCT	CAG	CAT	TGG	AGT	GAA	TGG	720
	Ser	Arg	Phe	Asn	Pro	Leu	Cys	Gly	Ser	Ala	Gln	His	Trp	Ser	Glu	Trp	
			205					210					215				
10	AGC	CAC	CCA	ATC	CAC	TGG	GGG	AGC	AAT	ACT	TCA	AAA	GAG	AAT	CCT	TTC	768
	Ser	His	Pro	Ile	His	Trp	Gly	Ser	Asn	Thr	Ser	Lys	Glu	Asn	Pro	Phe	
		220					225					230					
	CTG	TTT	GCA	TTG	GAA	GCC	GTG	GTT	ATC	TCT	GTT	GGC	TCC	ATG	GGA	TTG	816
	Leu	Phe	Ala	Leu	Glu	Ala	Val	Val	Ile	Ser	Val	Gly	Ser	Met	Gly	Leu	
		235				240					245				250		
15	ATT	ATC	AGC	CTT	CTC	TGT	GTG	TAT	TTC	TGG	CTG	GAA	CGG	ACG	ATG	CCC	864
	Ile	Ile	Ser	Leu	Leu	Cys	Val	Tyr	Phe	Trp	Leu	Glu	Arg	Thr	Met	Pro	
				255						260					265		
	CGA	ATT	CCC	ACC	CTG	AAG	AAC	CTA	GAG	GAT	CTT	GTT	ACT	GAA	TAC	CAC	912
	Arg	Ile	Pro	Thr	Leu	Lys	Asn	Leu	Glu	Asp	Leu	Val	Thr	Glu	Tyr	His	
			270						275					280			
20	GGG	AAC	TTT	TCG	GCC	TGG	AGT	GGT	GTG	TCT	AAG	GGA	CTG	GCT	GAG	AGT	960
	Gly	Asn	Phe	Ser	Ala	Trp	Ser	Gly	Val	Ser	Lys	Gly	Leu	Ala	Glu	Ser	
		285						290					295				
	CTG	CAG	CCA	GAC	TAC	AGT	GAA	CGA	CTC	TGC	CTC	GTC	AGT	GAG	ATT	CCC	1008
	Leu	Gln	Pro	Asp	Tyr	Ser	Glu	Arg	Leu	Cys	Leu	Val	Ser	Glu	Ile	Pro	
		300					305					310					
25	CCA	AAA	GGA	GGG	GCC	CTT	GGG	GAG	GGG	CCT	GGG	GCC	TCC	CCA	TGC	AAC	1056
	Pro	Lys	Gly	Gly	Ala	Leu	Gly	Glu	Gly	Pro	Gly	Ala	Ser	Pro	Cys	Asn	
		315				320					325				330		
	CAG	CAT	AGC	CCC	TAC	TGG	GCC	CCC	CCA	TGT	TAC	ACC	CTA	AAG	CCT	GAA	1104
	Gln	His	Ser	Pro	Tyr	Trp	Ala	Pro	Pro	Cys	Tyr	Thr	Leu	Lys	Pro	Glu	
				335						340					345		
30	ACC	TGA															1110
	Thr																
35																	
40																	
45																	
50																	
55																	

## INFORMATION FOR SEQ.ID.NO. 5

## Sequence characteristics

Length: 1044 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

## Feature

Key: mat\_peptide  
 Location: 1..1044

## Sequence description

SEQ.ID.NO.: 5

CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT	48
Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala	
1 5 10 15	
GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT	96
Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr	
20 25 30	
CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG	144
Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met	
35 40 45	
AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT	192
Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr	
50 55 60	
CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC	240
Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys	
65 70 75 80	
AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA	288
Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln	
85 90 95	
AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC	336
Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp	
100 105 110	
CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT	384
Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn	
115 120 125	
CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT	432
Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser	
130 135 140	
GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT	480
Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys	
145 150 155 160	
TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT	528
Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr	
165 170 175	
GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT	576
Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp	
180 185 190	
GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC	624
Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu	
195 200 205	
TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG	672
Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp	
210 215 220	
GGG AGC AAT ACT TCA AAA GAG AAT CCT TTC CTG TTT GCA TTG GAA GCC	720
Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala	
225 230 235 240	
GTG GTT ATC TCT GTT GGC TCC ATG GGA TTG ATT ATC AGC CTT CTC TGT	768

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Val Val Ile Ser Val Gly Ser Met Gly Leu Ile Ile Ser Leu Leu Cys  
 245 250 255  
 GTG TAT TTC TGG CTG GAA CGG ACG ATG CCC CGA ATT CCC ACC CTG AAG 816  
 Val Tyr Phe Trp Leu Glu Arg Thr Met Pro Arg Ile Pro Thr Leu Lys  
 260 265 270  
 AAC CTA GAG GAT CTT GTT ACT GAA TAC CAC GGG AAC TTT TCG GCC TGG 864  
 Asn Leu Glu Asp Leu Val Thr Glu Tyr His Gly Asn Phe Ser Ala Trp  
 275 280 285  
 AGT GGT GTG TCT AAG GGA CTG GCT GAG AGT CTG CAG CCA GAC TAC AGT 912  
 Ser Gly Val Ser Lys Gly Leu Ala Glu Ser Leu Gln Pro Asp Tyr Ser  
 290 295 300  
 GAA CGA CTC TGC CTC GTC AGT GAG ATT CCC CCA AAA GGA GGG GCC CTT 960  
 Glu Arg Leu Cys Leu Val Ser Glu Ile Pro Pro Lys Gly Gly Ala Leu  
 305 310 315 320  
 GGG GAG GGG CCT GGG GCC TCC CCA TGC AAC CAG CAT AGC CCC TAC TGG 1008  
 Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn Gln His Ser Pro Tyr Trp  
 325 330 335  
 GCC CCC CCA TGT TAC ACC CTA AAG CCT GAA ACC TGA 1044  
 Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu Thr  
 340 345

## INFORMATION FOR SEQ.ID.NO. 6

Sequence characteristics  
 Length: 759 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

Feature  
 Key: CDS  
 Location: 1..759

Feature  
 Key: sig\_peptide  
 Location: 1..66

Feature  
 Key: mat\_peptide  
 Location: 67..759

Sequence description  
 SEQ.ID.NO.: 6

ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG 48  
 Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu  
 -20 -15 -10  
 CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG 96  
 Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly  
 -5 1 5 10  
 AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC 144  
 Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp  
 15 20 25  
 TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG 192  
 Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val  
 30 35 40

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	TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC	240
	Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro	
	45 50 55	
5	CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT	288
	Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn	
	60 65 70	
	GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT	336
	Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr	
	75 80 85 90	
10	TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT	384
	Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe	
	95 100 105	
	GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG	432
	Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln	
	110 115 120	
	ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA	480
	Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu	
15	125 130 135	
	ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC	528
	Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn	
	140 145 150	
	AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC	576
	Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln Tyr Arg Thr Asp	
20	155 160 165	
	TGG GAC CAC AGC TGG ACT GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC	624
	Trp Asp His Ser Trp Thr Glu Gln Ser Val Asp Tyr Arg His Lys Phe	
	175 180 185	
	TCC TTG CCT AGT GTG GAT GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG	672
	Ser Leu Pro Ser Val Asp Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg	
	190 195 200	
25	AGC CGC TTT AAC CCA CTC TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG	720
	Ser Arg Phe Asn Pro Leu Cys Gly Ser Ala Gln His Trp Ser Glu Trp	
	205 210 215	
	AGC CAC CCA ATC CAC TGG GGG AGC AAT ACT TCA AAA TAG	759
	Ser His Pro Ile His Trp Gly Ser Asn Thr Ser Lys	
	220 225 230	

## INFORMATION FOR SEQ.ID.NO. 7

### Sequence characteristics

Length: 693 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

### Feature

Key: mat\_peptide  
 Location: 1..693

### Sequence description

SEQ.ID.NO.: 7

	CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT	48
	Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala	
	1 5 10 15	
50	GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT	96
	Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr	
	20 25 30	



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	CTG	CCC	CTC	CCA	GAG	GTT	CAG	TGT	TTT	GTG	TTC	AAT	GTC	GAG	TAC	ATG	144
	Leu	Pro	Leu	Pro	Glu	Val	Gln	Cys	Phe	Val	Phe	Asn	Val	Glu	Tyr	Met	
			35					40					45				
5	AAT	TGC	ACT	TGG	AAC	AGC	AGC	TCT	GAG	CCC	CAG	CCT	ACC	AAC	CTC	ACT	192
	Asn	Cys	Thr	Trp	Asn	Ser	Ser	Ser	Glu	Pro	Gln	Pro	Thr	Asn	Leu	Thr	
		50					55					60					
	CTG	CAT	TAT	TGG	TAC	AAG	AAC	TCG	GAT	AAT	GAT	AAA	GTC	CAG	AAG	TGC	240
	Leu	His	Tyr	Trp	Tyr	Lys	Asn	Ser	Asp	Asn	Asp	Lys	Val	Gln	Lys	Cys	
		65				70					75				80		
10	AGC	CAC	TAT	CTA	TTC	TCT	GAA	GAA	ATC	ACT	TCT	GGC	TGT	CAG	TTG	CAA	288
	Ser	His	Tyr	Leu	Phe	Ser	Glu	Glu	Ile	Thr	Ser	Gly	Cys	Gln	Leu	Gln	
					85				90					95			
	AAA	AAG	GAG	ATC	CAC	CTC	TAC	CAA	ACA	TTT	GTT	GTT	CAG	CTC	CAG	GAC	336
	Lys	Lys	Glu	Ile	His	Leu	Tyr	Gln	Thr	Phe	Val	Val	Gln	Leu	Gln	Asp	
				100					105				110				
15	CCA	CGG	GAA	CCC	AGG	AGA	CAG	GCC	ACA	CAG	ATG	CTA	AAA	CTG	CAG	AAT	384
	Pro	Arg	Glu	Pro	Arg	Arg	Gln	Ala	Thr	Gln	Met	Leu	Lys	Leu	Gln	Asn	
			115					120					125				
	CTG	GTG	ATC	CCC	TGG	GCT	CCA	GAG	AAC	CTA	ACA	CTT	CAC	AAA	CTG	AGT	432
	Leu	Val	Ile	Pro	Trp	Ala	Pro	Glu	Asn	Leu	Thr	Leu	His	Lys	Leu	Ser	
		130					135					140					
20	GAA	TCC	CAG	CTA	GAA	CTG	AAC	TGG	AAC	AAC	AGA	TTC	TTG	AAC	CAC	TGT	480
	Glu	Ser	Gln	Leu	Glu	Leu	Asn	Trp	Asn	Asn	Arg	Phe	Leu	Asn	His	Cys	
		145				150				155					160		
	TTG	GAG	CAC	TTG	GTG	CAG	TAC	CGG	ACT	GAC	TGG	GAC	CAC	AGC	TGG	ACT	528
	Leu	Glu	His	Leu	Val	Gln	Tyr	Arg	Thr	Asp	Trp	Asp	His	Ser	Trp	Thr	
				165					170						175		
25	GAA	CAA	TCA	GTG	GAT	TAT	AGA	CAT	AAG	TTC	TCC	TTG	CCT	AGT	GTG	GAT	576
	Glu	Gln	Ser	Val	Asp	Tyr	Arg	His	Lys	Phe	Ser	Leu	Pro	Ser	Val	Asp	
				180					185					190			
	GGG	CAG	AAA	CGC	TAC	ACG	TTT	CGT	GTT	CGG	AGC	CGC	TTT	AAC	CCA	CTC	624
	Gly	Gln	Lys	Arg	Tyr	Thr	Phe	Arg	Val	Arg	Ser	Arg	Phe	Asn	Pro	Leu	
		195						200					205				
30	TGT	GGA	AGT	GCT	CAG	CAT	TGG	AGT	GAA	TGG	AGC	CAC	CCA	ATC	CAC	TGG	672
	Cys	Gly	Ser	Ala	Gln	His	Trp	Ser	Glu	Trp	Ser	His	Pro	Ile	His	Trp	
		210					215					220					
	GGG	AGC	AAT	ACT	TCA	AAA	TAG										693
	Gly	Ser	Asn	Thr	Ser	Lys											
35		225				230											

INFORMATION FOR SEQ.ID.NO. 8

40 Sequence characteristics  
 Length: 20  
 Type: amino acids  
 Topology: linear

45 Sequence description  
 SEQ.ID.NO.: 8

	Leu	Asn	Thr	Thr	Ile	Leu	Thr	Pro	Asn	Gly	Asn	Glu	Asp	Thr	Thr	Ala	
	1				5					10					15		
50	Asp	Phe	Phe	Leu													
				20													

55

INFORMATION FOR SEQ.ID.NO. 9

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 9

ATACTGACGC CGAATGG

TT	A	A	A
C		T	T
		C	C

INFORMATION FOR SEQ.ID.NO. 10

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 10

ATACTGACGC CGAACGG

TT	A	A	A
C		T	T
		C	C

INFORMATION FOR SEQ.ID.NO. 11

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 11

ATACTTACGC CGAATGG

T	C	A	A
C		T	T
		C	C

## INFORMATION FOR SEQ.ID.NO. 12

## Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

## Sequence description

SEQ.ID.NO.: 12

ATACTTACGC CGAACGG

T	C	A	A
C		T	T
		C	C

## INFORMATION FOR SEQ.ID.NO. 13

## Sequence characteristics

Length: 22 bases  
Type: nucleic acid  
Topology: linear

## Sequence description

SEQ.ID.NO.: 13

AAAAAAAAGA GGGCCTAGGC GC

GG	AT	CAT
	T	T
	C	C

## INFORMATION FOR SEQ.ID.NO. 14

## Sequence characteristics

Length: 22 bases  
Type: nucleic acid  
Topology: linear

## Sequence description

SEQ.ID.NO.: 14

AAGAAAAAGA GGGCCTAGGC GC

GG	AT	CAT
	T	T
	C	C

INFORMATION FOR SEQ.ID.NO. 15

Sequence characteristics

Length: 25 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 15

5'-AGCTCGAGCG CCATGTTGAA GCCAT-3'

INFORMATION FOR SEQ.ID.NO. 16

Sequence characteristics

Length: 28 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 16

5'-AACTCGAGAG GATTCTATTT TGAAGTAT-3'

SEQUENCE LISTING

5       APPLICANT:  
           Name:               Ajinomoto Co., Inc.  
           Street:            15-1, Kyobashi-1-chome  
           City:              Chuo-ku Tokyo  
           State               Japan  
 10       Postal Code:        104  
           Telephone:        (03) 5250-8111  
           Telefax:           (03) 5250-8347  
           Telex:             J2808

15       APPLICANT:  
           Name:               Kazuo Sugamura  
           Street:            27-8, Asahigaoka 1-chome, Aoba-ku  
           City:              Miyagi-ken  
           Postal Code:       100  
 20       Telephone:        (03) 5250-8111  
           Telefax:           (03) 5250-8347  
           Telex:             J2808

          TITLE OF THE INVENTION:   IL-2 RECEPTOR  $\gamma$ -CHAIN MOLECULE

25       NUMBER OF SEQUENCES:   16

          COMPUTER READABLE FORM  
           Medium type:       Diskette  
           Computer:          IBM-compatible  
 30       Operating system:   MS-DOS 5.0  
           Software:          Microsoft Word

          CURRENT APPLICATION DATA:  
           Application number: 93 106 561.9

35       PRIOR APPLICATION DATA  
           Application number: 104947/1992  
           Filing date:       April, 23  
           classification:    12

40       INFORMATION FOR SEQ.ID.NO. 1  
           Sequence characteristics  
           Length:            1062 base pairs  
           Type:              nucleic acid  
           Strandedness:      single  
 45       Topology:            linear

          Molecule type:       DNA

50       Original source  
           Organism:           Homo sapiens  
           Cell type:          Lymphocyte

55

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## Sequence description

SEQ.ID.NO.:

1

	GAAGAGCAAG	CGCCATGTTG	AAGCCATCAT	TACCATTAC	ATCCCTCTTA	TTCCTGCAGC	60
5	TGCCCCTGCT	GGGAGTGGGG	CTGAACACGA	CAATTCTGAC	GCCCAATGGG	AATGAAGACA	120
	CCACAGCTGA	TTTCTTCCTG	ACCACTATGC	CCACTGACTC	CCTCAGCGTT	TCCACTCTGC	180
	CCCTCCCAGA	GGTTCAGTGT	TTTGTGTTCA	ATGTCGAGTA	CATGAATTGC	ACTTGGAAACA	240
	GCAGCTCTGA	GCCCCAGCCT	ACCAACCTCA	CTCTGCATTA	TTGGTACAAG	AACTCGGATA	300
	ATGATAAAGT	CCAGAAGTGC	AGCCACTATC	TATTCTCTGA	AGAAATCACT	TCTGGCTGTC	360
	AGTTGCAAAA	AAAGGAGATC	CACCTCTACC	AAACATTTGT	TGTTGAGCTC	CAGGACCCAC	420
10	GGGAACCCAG	GAGACAGGCC	ACACAGATGC	TAAAACCTGA	GAATCTGGTG	ATCCCCTGGG	480
	CTCCAGAGAA	CCTAACACTT	CACAACTGA	GTGAATCCCA	GCTAGAACTG	AACTGGAACA	540
	ACAGATTCTT	GAACCACTGT	TTGGAGCACT	TGGTGCAGTA	CCGGACTGAC	TGGGACCACA	600
	GCTGGACTGA	ACAACTCAGT	GATTATAGAC	ATAAGTTCTC	CTTGCCTAGT	GTGGATGGGC	660
	AGAAACGCTA	CACGTTTCGT	GTTCCGAGCC	GCTTTAACCC	ACTCTGTGGA	AGTGCTCAGC	720
	ATTGGAGTGA	ATGGAGCCAC	CCAATCCACT	GGGGGAGCAA	TACTTCAAAA	GAGAATCCTT	780
15	TCCTGTTTGC	ATTGGAAGCC	GTGGTTATCT	CTGTTGGCTC	CATGGGATTG	ATTATCAGCC	840
	TTCTCTGTGT	GTATTTCTGG	CTGGAACGGA	CGATGCCCGG	AATTCCCACC	CTGAAGAACC	900
	TAGAGGATCT	TGTTACTGAA	TACCACGGGA	ACTTTTCGGC	CTGGAGTGGT	GTGTCTAAGG	960
	GACTGGCTGA	GAGTCTGCAG	CCAGACTACA	GTGAACGACT	CTGCCTCGTC	AGTGAGATTG	1020
	CCCCAAAAGG	AGGGGCCCTT	GGGGAGGGGC	CTGGGGCCTC	CC		1062

20

## INFORMATION FOR SEQ.ID.NO. 2

## Sequence characteristics

25	Length:	1393 base pairs
	Type:	nucleic acid
	Strandedness:	single
	Topology:	linear

30	Molecule type:	DNA (cDNA)
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## Original source

	Organism:	Homo sapiens
	Cell type:	Lymphocyte

## 35 Sequence description

SEQ.ID.NO.:

2

	GGGCTGAACA	CGACAATTCT	GACGCCCAAT	GGGAATGAAG	ACACCACAGC	TGATTTCTTC	60
	CTGACCACTA	TGCCCCTGGA	CTCCCTCAGC	GTTCCTCACTC	TGCCCCTCCC	AGAGGTTTCTC	120
40	TGTTTTGTGT	TCAATGTCGA	GTACATGAAT	TGCACTTGGA	ACAGCAGCTC	TGAGCCCCAG	180
	CCTACCAACC	TCACTCTGCA	TTATTGGTAC	AAGAATCGG	ATAATGATAA	AGTCCAGAAG	240
	TGCAGCCACT	ATCTATTCTC	TGAAGAAATC	ACTTCTGGCT	GTCAGTTGCA	AAAAAAGGAG	300
	ATCCACCTCT	ACCAAACATT	TGTTGTTTCT	CTCCAGGACC	CACGGGAACC	CAGGAGACAG	360
	GCCACACAGA	TGCTAAAAC	GCAGAACTCT	GTGATCCCCT	GGGCTCCAGA	GAACCTAACA	420
	CTTCACAAAC	TGAGTGAATC	CCAGCTAGAA	CTGAACCTGGA	ACAACAGATT	CTTGAACCAC	480
45	TGTTTGGAGC	ACTTGGTGCA	GTACCGGACT	GACTGGGACC	ACAGCTGGAC	TGAACAATCA	540
	GTGGATTATA	GACATAAGTT	CTCCTTGCTT	AGTGTGGATG	GGCAGAAACG	CTACACGTTT	600
	CGTGTTCGGA	GCCGCTTTAA	CCCCTCTGCT	GGAAGTGCTC	AGCATTGGAG	TGAATGGAGC	660
	CACCCAATCC	ACTGGGGGAG	CAATACTTCA	AAAGAGAATC	CTTCCTGTT	TGCATTGGAA	720
	GCCGTGGTTA	TCTCTGTTGG	CTCCATGGGA	TTGATTATCA	GCCTTCTCTG	TGTGTATTTT	780
	TGGCTGGAAC	GGACGATGCC	CCGAATTTCC	ACCCTGAAGA	ACCTAGAGGA	TCTTGTACTT	840
50	GAATACCACG	GGAACCTTTT	GGCCTGGAGT	GGTGTGCTTA	AGGGACTGGC	TGAGAGTCTG	900
	CAGCCAGACT	ACAGTGAACG	ACTCTGCCTC	GTCAGTGAGA	TTCCCCCAA	AGGAGGGGCC	960
	CTTGGGGAGG	GGCCTGGGGC	CTCCCCATGC	AACCAGCATA	GCCCCTACTG	GGCCCCCCCC	1020

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```

5  TGTACACCC TAAAGCCTGA AACCTGAACC CCAATCCTCT GACAGAAGAA CCCCAGGGTC 1080
   CTGTAGCCCT AAGTGGTACT AACTTTCCTT CATTCACCCC ACCTGCGTCT CATACTCACC 1140
   TCACCCCACT GTGGCTGATT TGGAAATTTG TGCCCCCATG TAAGCACCCC TTCATTTGGC 1200
   ATTCCCACT TGAGAATTAC CCTTTTGCCC CGAACATGTT TTTCTTCTCC CTCAGTCTGG 1260
   CCCTTCCTTT TCGCAGGATT CTTCTCCCT CCCTCTTCC CTCCCTTCCT CTTTCCATCT 1320
   ACCCTCCGAT TGTTCCTGAA CCGATGAGAA ATAAAGTTTC TGTTGATAAT CATCAAAAAA 1380
   AAAAAAAAA AAA 1393

```

# 10 INFORMATION FOR SEQ.ID.NO. 3

## Sequence characteristics

```

15 Length:      1470 base pairs
   Type:       nucleic acid
   Strandedness: single
   Topology:   linear

```

Molecule type: DNA

## 20 Feature

```

   Key:        CDS
   Location:    15..1124

```

## 25 Feature

```

   Key:        sig_peptide
   Location:    15..80

```

## 30 Feature

```

   Key:        mat_peptide
   Location:    81..1124

```

## Sequence description

SEQ.ID.NO.: 3

```

35 GAAGAGCAAG CGCC ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA 50
    Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu
    -20 -15
    TTC CTG CAG CTG CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG 98
    Phe Leu Gln Leu Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu
    -10 -5 1 5
    40 ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT 146
    Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr
    10 15 20
    ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT 194
    Met Pro Thr Asp Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val
    25 30 35
    45 CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC 242
    Gln Cys Phe Val Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser
    40 45 50
    AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG 290
    Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys
    55 60 65 70
    50 AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT 338
    Asn Ser Asp Asn Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser
    75 80 85

```



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	GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC	386
	Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu	
	90 95 100	
5	TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA	434
	Tyr Gln Thr Phe Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg	
	105 110 115	
	CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT	482
	Gln Ala Thr Gln Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala	
	120 125 130	
10	CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG	530
	Pro Glu Asn Leu Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu	
	135 140 145 150	
	AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG	578
	Asn Trp Asn Asn Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln	
	155 160 165	
15	TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT GAA CAA TCA GTG GAT TAT	626
	Tyr Arg Thr Asp Trp Asp His Ser Trp Thr Glu Gln Ser Val Asp Tyr	
	170 175 180	
	AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT GGG CAG AAA CGC TAC ACG	674
	Arg His Lys Phe Ser Leu Pro Ser Val Asp Gly Gln Lys Arg Tyr Thr	
	185 190 195	
20	TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC TGT GGA AGT GCT CAG CAT	722
	Phe Arg Val Arg Ser Arg Phe Asn Pro Leu Cys Gly Ser Ala Gln His	
	200 205 210	
	TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG GGG AGC AAT ACT TCA AAA	770
	Trp Ser Glu Trp Ser His Pro Ile His Trp Gly Ser Asn Thr Ser Lys	
	215 220 225 230	
25	GAG AAT CCT TTC CTG TTT GCA TTG GAA GCC GTG GTT ATC TCT GTT GGC	818
	Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala Val Val Ile Ser Val Gly	
	235 240 245	
	TCC ATG GGA TTG ATT ATC AGC CTT CTC TGT GTG TAT TTC TGG CTG GAA	866
	Ser Met Gly Leu Ile Ile Ser Leu Leu Cys Val Tyr Phe Trp Leu Glu	
	250 255 260	
30	CGG ACG ATG CCC CGA ATT CCC ACC CTG AAG AAC CTA GAG GAT CTT GTT	914
	Arg Thr Met Pro Arg Ile Pro Thr Leu Lys Asn Leu Glu Asp Leu Val	
	265 270 275	
	ACT GAA TAC CAC GGG AAC TTT TCG GCC TGG AGT GGT GTG TCT AAG GGA	962
	Thr Glu Tyr His Gly Asn Phe Ser Ala Trp Ser Gly Val Ser Lys Gly	
	280 285 290	
35	CTG GCT GAG AGT CTG CAG CCA GAC TAC AGT GAA CGA CTC TGC CTC GTC	1010
	Leu Ala Glu Ser Leu Gln Pro Asp Tyr Ser Glu Arg Leu Cys Leu Val	
	295 300 305 310	
	AGT GAG ATT CCC CCA AAA GGA GGG GCC CTT GGG GAG GGG CCT GGG GCC	1058
	Ser Glu Ile Pro Pro Lys Gly Gly Ala Leu Gly Glu Gly Pro Gly Ala	
	315 320 325	
40	TCC CCA TGC AAC CAG CAT AGC CCC TAC TGG GCC CCC CCA TGT TAC ACC	1106
	Ser Pro Cys Asn Gln His Ser Pro Tyr Trp Ala Pro Pro Cys Tyr Thr	
	330 335 340	
	CTA AAG CCT GAA ACC TGAACCCCAA TCCTCTGACA GAAGAACCCC AGGGTCCTGT	1161
	Leu Lys Pro Glu Thr	
	345	
45	AGCCCTAAGT GGTACTAACT TTCCTTCATT CAACCCACCT GCGTCTCATA CTCACCTCAC	1221
	CCCACTGTGG CTGATTTGGA ATTTTGTGCC CCCATGTAAG CACCCCTTCA TTTGGCATTC	1281
	CCCACTTGAG AATTACCCTT TTGCCCCGAA CATGTTTTTC TTCTCCCTCA GTCTGGCCCT	1341
	TCCTTTTCGC AGGATTCTTC CTCCCTCCCT CTTTCCCTCC CTTCCTCTTT CCATCTACCC	1401
	TCCGATTGTT CCTGAACCGA TGAGAAATAA AGTTTCTGTT GATAATCATC AAAAAAAAAA	1461
50	AAAAAAAAA	1470

## INFORMATION FOR SEQ.ID.NO. 4

## Sequence characteristics

Length: 1110 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

## Feature

Key: CDS  
 Location: 1..1110

## Feature

Key: sig\_peptide  
 Location: 1..66

## Feature

Key: mat\_peptide  
 Location: 67..1110

## Sequence description

SEQ.ID.NO.: 4

ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG	48
Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu	
-20 -15 -10	
CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG	96
Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly	
-5 1 5 10	
AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC	144
Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp	
15 20 25	
TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG	192
Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val	
30 35 40	
TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC	240
Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro	
45 50 55	
CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT	288
Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn	
60 65 70	
GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT	336
Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr	
75 80 85 90	
TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT	384
Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe	
95 100 105	
GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG	432
Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln	
110 115 120	
ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA	480
Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu	
125 130 135	

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	ACA	CTT	CAC	AAA	CTG	AGT	GAA	TCC	CAG	CTA	GAA	CTG	AAC	TGG	AAC	AAC	528
	Thr	Leu	His	Lys	Leu	Ser	Glu	Ser	Gln	Leu	Glu	Leu	Asn	Trp	Asn	Asn	
	140						145				150						
5	AGA	TTC	TTG	AAC	CAC	TGT	TTG	GAG	CAC	TTG	GTG	CAG	TAC	CGG	ACT	GAC	576
	Arg	Phe	Leu	Asn	His	Cys	Leu	Glu	His	Leu	Val	Gln	Tyr	Arg	Thr	Asp	
	155					160					165					170	
	TGG	GAC	CAC	AGC	TGG	ACT	GAA	CAA	TCA	GTG	GAT	TAT	AGA	CAT	AAG	TTC	624
	Trp	Asp	His	Ser	Trp	Thr	Glu	Gln	Ser	Val	Asp	Tyr	Arg	His	Lys	Phe	
					175					180					185		
10	TCC	TTG	CCT	AGT	GTG	GAT	GGG	CAG	AAA	CGC	TAC	ACG	TTT	CGT	GTT	CGG	672
	Ser	Leu	Pro	Ser	Val	Asp	Gly	Gln	Lys	Arg	Tyr	Thr	Phe	Arg	Val	Arg	
				190					195					200			
	AGC	CGC	TTT	AAC	CCA	CTC	TGT	GGA	AGT	GCT	CAG	CAT	TGG	AGT	GAA	TGG	720
	Ser	Arg	Phe	Asn	Pro	Leu	Cys	Gly	Ser	Ala	Gln	His	Trp	Ser	Glu	Trp	
			205					210					215				
15	AGC	CAC	CCA	ATC	CAC	TGG	GGG	AGC	AAT	ACT	TCA	AAA	GAG	AAT	CCT	TTC	768
	Ser	His	Pro	Ile	His	Trp	Gly	Ser	Asn	Thr	Ser	Lys	Glu	Asn	Pro	Phe	
			220				225					230					
	CTG	TTT	GCA	TTG	GAA	GCC	GTG	GTT	ATC	TCT	GTT	GGC	TCC	ATG	GGA	TTG	816
	Leu	Phe	Ala	Leu	Glu	Ala	Val	Val	Ile	Ser	Val	Gly	Ser	Met	Gly	Leu	
						240					245					250	
20	ATT	ATC	AGC	CTT	CTC	TGT	GTG	TAT	TTC	TGG	CTG	GAA	CGG	ACG	ATG	CCC	864
	Ile	Ile	Ser	Leu	Leu	Cys	Val	Tyr	Phe	Trp	Leu	Glu	Arg	Thr	Met	Pro	
					255					260					265		
	CGA	ATT	CCC	ACC	CTG	AAG	AAC	CTA	GAG	GAT	CTT	GTT	ACT	GAA	TAC	CAC	912
	Arg	Ile	Pro	Thr	Leu	Lys	Asn	Leu	Glu	Asp	Leu	Val	Thr	Glu	Tyr	His	
				270				275					280				
25	GGG	AAC	TTT	TCG	GCC	TGG	AGT	GGT	GTG	TCT	AAG	GGA	CTG	GCT	GAG	AGT	960
	Gly	Asn	Phe	Ser	Ala	Trp	Ser	Gly	Val	Ser	Lys	Gly	Leu	Ala	Glu	Ser	
			285				290					295					
	CTG	CAG	CCA	GAC	TAC	AGT	GAA	CGA	CTC	TGC	CTC	GTC	AGT	GAG	ATT	CCC	1008
	Leu	Gln	Pro	Asp	Tyr	Ser	Glu	Arg	Leu	Cys	Leu	Val	Ser	Glu	Ile	Pro	
			300				305					310					
30	CCA	AAA	GGA	GGG	GCC	CTT	GGG	GAG	GGG	CCT	GGG	GCC	TCC	CCA	TGC	AAC	1056
	Pro	Lys	Gly	Gly	Ala	Leu	Gly	Glu	Gly	Pro	Gly	Ala	Ser	Pro	Cys	Asn	
			315			320					325				330		
	CAG	CAT	AGC	CCC	TAC	TGG	GCC	CCC	CCA	TGT	TAC	ACC	CTA	AAG	CCT	GAA	1104
	Gln	His	Ser	Pro	Tyr	Trp	Ala	Pro	Pro	Cys	Tyr	Thr	Leu	Lys	Pro	Glu	
				335					340					345			
35	ACC	TGA															1110
	Thr																

INFORMATION FOR SEQ.ID.NO. 5

Sequence characteristics

Length: 1044 base pairs  
 Type: nucleic acid  
 Strandedness: single  
 Topology: linear

Molecule type: DNA

Feature

Key: mat\_peptide  
 Location: 1..1044

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Sequence description

SEQ.ID.NO.:

5

5	CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT	48
	Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala	
	1 5 10 15	
	GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT	96
	Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr	
	20 25 30	
10	CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG	144
	Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met	
	35 40 45	
	AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT	192
	Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr	
	50 55 60	
15	CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC	240
	Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys	
	65 70 75 80	
	AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA	288
	Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln	
	85 90 95	
20	AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC	336
	Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp	
	100 105 110	
	CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT	384
	Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn	
	115 120 125	
25	CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT	432
	Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser	
	130 135 140	
	GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT	480
	Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys	
	145 150 155 160	
30	TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT	528
	Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr	
	165 170 175	
	GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT	576
	Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp	
	180 185 190	
35	GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC	624
	Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu	
	195 200 205	
	TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG	672
	Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp	
	210 215 220	
40	GGG AGC AAT ACT TCA AAA GAG AAT CCT TTC CTG TTT GCA TTG GAA GCC	720
	Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala	
	225 230 235 240	
	GTG GTT ATC TCT GTT GGC TCC ATG GGA TTG ATT ATC AGC CTT CTC TGT	768
	Val Val Ile Ser Val Gly Ser Met Gly Leu Ile Ile Ser Leu Leu Cys	
	245 250 255	
45	GTG TAT TTC TGG CTG GAA CGG ACG ATG CCC CGA ATT CCC ACC CTG AAG	816
	Val Tyr Phe Trp Leu Glu Arg Thr Met Pro Arg Ile Pro Thr Leu Lys	
	260 265 270	
	AAC CTA GAG GAT CTT GTT ACT GAA TAC CAC GGG AAC TTT TCG GCC TGG	864
	Asn Leu Glu Asp Leu Val Thr Glu Tyr His Gly Asn Phe Ser Ala Trp	
	275 280 285	
50	AGT GGT GTG TCT AAG GGA CTG GCT GAG AGT CTG CAG CCA GAC TAC AGT	912
	Ser Gly Val Ser Lys Gly Leu Ala Glu Ser Leu Gln Pro Asp Tyr Ser	
	290 295 300	

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```

GAA CGA CTC TGC CTC GTC AGT GAG ATT CCC CCA AAA GGA GGG GCC CTT 960
Glu Arg Leu Cys Leu Val Ser Glu Ile Pro Pro Lys Gly Gly Ala Leu
305          310          315          320
5  GGG GAG GGG CCT GGG GCC TCC CCA TGC AAC CAG CAT AGC CCC TAC TGG 1008
   Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn Gln His Ser Pro Tyr Trp
           325          330          335
GCC CCC CCA TGT TAC ACC CTA AAG CCT GAA ACC TGA          1044
Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu Thr
           340          345

```

## INFORMATION FOR SEQ.ID.NO. 6

### Sequence characteristics

```

Length:      759 base pairs
Type:        nucleic acid
Strandedness: single
Topology:    linear

```

Molecule type: DNA

### Feature

```

Key:      CDS
Location: 1..759

```

### Feature

```

Key:      sig_peptide
Location: 1..66

```

### Feature

```

Key:      mat_peptide
Location: 67..759

```

### Sequence description

```

SEQ.ID.NO.: 6

```

```

ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG 48
Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu
-20          -15          -10
40 CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG 96
   Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly
   -5          1          5          10
AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC 144
Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp
           15          20          25
45 TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG 192
   Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val
           30          35          40
TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC 240
Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro
           45          50          55
50 CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT 288
   Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn
           60          65          70

```

5 GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT 336  
 Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr 90  
 75 80 85  
 TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT 384  
 Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe 105  
 95 100  
 GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG 432  
 Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln 120  
 110 115  
 10 ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA 480  
 Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu 135  
 125 130  
 ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC 528  
 Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn 150  
 140 145  
 15 AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC 576  
 Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln Tyr Arg Thr Asp 170  
 155 160 165  
 TGG GAC CAC AGC TGG ACT GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC 624  
 Trp Asp His Ser Trp Thr Glu Gln Ser Val Asp Tyr Arg His Lys Phe 185  
 175 180  
 20 TCC TTG CCT AGT GTG GAT GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG 672  
 Ser Leu Pro Ser Val Asp Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg 200  
 190 195  
 AGC CGC TTT AAC CCA CTC TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG 720  
 Ser Arg Phe Asn Pro Leu Cys Gly Ser Ala Gln His Trp Ser Glu Trp 215  
 205 210 215  
 25 AGC CAC CCA ATC CAC TGG GGG AGC AAT ACT TCA AAA TAG 759  
 Ser His Pro Ile His Trp Gly Ser Asn Thr Ser Lys 230  
 220 225 230

# 30 INFORMATION FOR SEQ.ID.NO. 7

## Sequence characteristics

Length: 693 base pairs  
 Type: nucleic acid  
 35 Strandedness: single  
 Topology: linear

Molecule type: DNA

## 40 Feature

Key: mat\_peptide  
 Location: 1..693

## Sequence description

45 SEQ.ID.NO.: 7

CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT 48  
 Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala 15  
 1 5 10  
 50 GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT 96  
 Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr 30  
 20 25 30

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CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG 144  
 Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met  
                   35                  40                  45  
 5 AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT 192  
 Asn Cys Thr Trp Asn Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr  
                   50                  55                  60  
 CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC 240  
 Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys  
                   65                  70                  75                  80  
 10 AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA 288  
 Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln  
                   85                  90                  95  
 AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC 336  
 Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp  
                   100                  105                  110  
 15 CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT 384  
 Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn  
                   115                  120                  125  
 CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT 432  
 Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser  
                   130                  135                  140  
 20 GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT 480  
 Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys  
                   145                  150                  155                  160  
 TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT 528  
 Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr  
                   165                  170                  175  
 25 GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT 576  
 Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp  
                   180                  185                  190  
 GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC 624  
 Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu  
                   195                  200                  205  
 30 TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG 672  
 Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp  
                   210                  215                  220  
 GGG AGC AAT ACT TCA AAA TAG 693  
 Gly Ser Asn Thr Ser Lys  
                   225                  230

INFORMATION FOR SEQ.ID.NO. 8

Sequence characteristics  
 Length: 20  
 Type: amino acids  
 Topology: linear

Sequence description  
 SEQ.ID.NO.: 8

Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala  
 1                  5                  10                  15  
 Asp Phe Phe Leu  
                   20



INFORMATION FOR SEQ.ID.NO. 9

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 9

ATHYTRACNC CNAATGG

INFORMATION FOR SEQ.ID.NO. 10

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 10

ATHYTRACNC CNAACGG

INFORMATION FOR SEQ.ID.NO. 11

Sequence characteristics

Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 11

ATHCTYACNC CNAATGG

INFORMATION FOR SEQ.ID.NO. 12

Sequence characteristics

5 Length: 17 bases  
Type: nucleic acid  
Topology: linear

Sequence description

10 SEQ.ID.NO.: 12

ATHCTYACNC CNAACGG

15

INFORMATION FOR SEQ.ID.NO. 13

Sequence characteristics

20 Length: 22 bases  
Type: nucleic acid  
Topology: linear

Sequence description

25 SEQ.ID.NO.: 13

AAAAARRANW SNKCCTAGGC GC

30

INFORMATION FOR SEQ.ID.NO. 14

Sequence characteristics

35 Length: 22 bases  
Type: nucleic acid  
Topology: linear

Sequence description

40 SEQ.ID.NO.: 14

AAGAARRANW SNKCCTAGGC GC

45

50

55

INFORMATION FOR SEQ.ID.NO. 15

Sequence characteristics

Length: 25 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 15

AGCTCGAGCG CCATGTTGAA GCCAT

INFORMATION FOR SEQ.ID.NO. 16

Sequence characteristics

Length: 28 bases  
Type: nucleic acid  
Topology: linear

Sequence description

SEQ.ID.NO.: 16 ✓

AACTCGAGAG GATTCTATTT TGAAGTAT

Claims

1. An Interleukin-2 receptor  $\gamma$ -chain polypeptide, which is substantially free of the other components of the Interleukin-2 receptor.
2. A human Interleukin-2 receptor  $\gamma$ -chain polypeptide, which is substantially free of the  $\alpha$ - and the  $\beta$ -chain.
3. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to claim 1 or claim 2, which is selected from the following group:
  - (a) a polypeptide having the following amino acid sequence: (Seq ID. No.4)

Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu  
 -20 -15 -10  
 Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly  
 -5 1 5 10  
 5 Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp  
 15 20 25  
 Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val  
 30 35 40  
 Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro  
 45 50 55  
 10 Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn  
 60 65 70  
 Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr  
 75 80 85 90  
 15 Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe  
 95 100 105  
 Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln  
 110 115 120  
 Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu  
 125 130 135  
 20 Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn  
 140 145 150  
 Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln Tyr Arg Thr Asp  
 155 160 165 170  
 Trp Asp His Ser Trp Thr Glu Gln Ser Val Asp Tyr Arg His Lys Phe  
 175 180 185  
 25 Ser Leu Pro Ser Val Asp Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg  
 190 195 200  
 Ser Arg Phe Asn Pro Leu Cys Gly Ser Ala Gln His Trp Ser Glu Trp  
 205 210 215  
 Ser His Pro Ile His Trp Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe  
 220 225 230  
 30  
 35 Leu Phe Ala Leu Glu Ala Val Val Ile Ser Val Gly Ser Met Gly Leu  
 235 240 245 250  
 Ile Ile Ser Leu Leu Cys Val Tyr Phe Trp Leu Glu Arg Thr Met Pro  
 255 260 265  
 Arg Ile Pro Thr Leu Lys Asn Leu Glu Asp Leu Val Thr Glu Tyr His  
 270 275 280  
 40 Gly Asn Phe Ser Ala Trp Ser Gly Val Ser Lys Gly Leu Ala Glu Ser  
 285 290 295  
 Leu Gln Pro Asp Tyr Ser Glu Arg Leu Cys Leu Val Ser Glu Ile Pro  
 300 305 310  
 Pro Lys Gly Gly Ala Leu Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn  
 315 320 325 330  
 45 Gln His Ser Pro Tyr Trp Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu  
 335 340 345  
 Thr

(b) a polypeptide, which is deficient in one or more amino acids;

(c) a polypeptide, in which in respect to (a) and/or (b) one or more amino acids are replaced;

(d) a fusion polypeptide comprising a polypeptide according to (a), (b) or (c).

(e) a polypeptide, which is an allelic derivative of a polypeptide according to (a), (b), (c) or (d).

4. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to claim 1 or claim 2, which is selected from the following group:

(a) a polypeptide having the following amino acid sequence: (Seq. Id. No. 5)

Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala  
 1 5 10 15  
 Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr  
 20 25 30  
 Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met  
 35 40 45  
 Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr  
 50 55 60  
 Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys  
 65 70 75 80  
 Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln  
 85 90 95  
 Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp  
 100 105 110  
 Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn  
 115 120 125  
 Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser  
 130 135 140  
 Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys  
 145 150 155 160  
 Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr  
 165 170 175  
 Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp  
 180 185 190

25

Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu  
 195 200 205  
 Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp  
 210 215 220  
 Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala  
 225 230 235 240  
 Val Val Ile Ser Val Gly Ser Met Gly Leu Ile Ile Ser Leu Leu Cys  
 245 250 255  
 Val Tyr Phe Trp Leu Glu Arg Thr Met Pro Arg Ile Pro Thr Leu Lys  
 260 265 270  
 Asn Leu Glu Asp Leu Val Thr Glu Tyr His Gly Asn Phe Ser Ala Trp  
 275 280 285  
 Ser Gly Val Ser Lys Gly Leu Ala Glu Ser Leu Gln Pro Asp Tyr Ser  
 290 295 300  
 Glu Arg Leu Cys Leu Val Ser Glu Ile Pro Pro Lys Gly Gly Ala Leu  
 305 310 315 320  
 Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn Gln His Ser Pro Tyr Trp  
 325 330 335  
 Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu Thr  
 340 345

45

- (b) a polypeptide, which is deficient in one or more amino acids;  
 (c) a polypeptide, in which in respect to (a) and/or (b) one or more amino acids are replaced;  
 (d) a fusion polypeptide comprising a polypeptide according to (a), (b) or (c);  
 (e) a polypeptide, which is an allelic derivative of a polypeptide according to (a), (b), (c) or (d).

50

5. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to claim 1 or claim 2, which is selected from the following group:

(a) a polypeptide having the following amino acid sequence: (Seq. Id. No. 6)

55

Met Leu Lys Pro Ser Leu Pro Phe Thr Ser Leu Leu Phe Leu Gln Leu  
 -20 -15 -10  
 Pro Leu Leu Gly Val Gly Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly  
 -5 1 5 10  
 5 Asn Glu Asp Thr Thr Ala Asp Phe Phe Leu Thr Thr Met Pro Thr Asp  
 15 20 25  
 Ser Leu Ser Val Ser Thr Leu Pro Leu Pro Glu Val Gln Cys Phe Val  
 30 35 40  
 Phe Asn Val Glu Tyr Met Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro  
 45 50 55  
 10 Gln Pro Thr Asn Leu Thr Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn  
 60 65 70  
 Asp Lys Val Gln Lys Cys Ser His Tyr Leu Phe Ser Glu Glu Ile Thr  
 75 80 85 90  
 Ser Gly Cys Gln Leu Gln Lys Lys Glu Ile His Leu Tyr Gln Thr Phe  
 95 100 105  
 15 Val Val Gln Leu Gln Asp Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln  
 110 115 120  
  
 20 Met Leu Lys Leu Gln Asn Leu Val Ile Pro Trp Ala Pro Glu Asn Leu  
 125 130 135  
 Thr Leu His Lys Leu Ser Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn  
 140 145 150  
 25 Arg Phe Leu Asn His Cys Leu Glu His Leu Val Gln Tyr Arg Thr Asp  
 155 160 165 170  
 Trp Asp His Ser Trp Thr Glu Gln Ser Val Asp Tyr Arg His Lys Phe  
 175 180 185  
 Ser Leu Pro Ser Val Asp Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg  
 190 195 200  
 30 Ser Arg Phe Asn Pro Leu Cys Gly Ser Ala Gln His Trp Ser Glu Trp  
 205 210 215  
 Ser His Pro Ile His Trp Gly Ser Asn Thr Ser Lys  
 220 225 230

- 35 (b) a polypeptide, which is deficient in one or more amino acids;  
 (c) a polypeptide, in which in respect to (a) and/or (b) one or more amino acids are replaced;  
 (d) a fusion polypeptide comprising a polypeptide according to (a), (b) or (c).  
 (e) a polypeptide, which is an allelic derivative of a polypeptide according to (a), (b), (c) or (d);  
 (f) a polypeptide, which lacks the signal peptide with respect to (a), (b), (c) or (e);  
 40 (g) a polypeptide, comprises the sequence in (a) of from - 22 (Met) to -1 (Gly).

6. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to any of the preceding claims, which is water soluble.  
 45 7. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to any of the preceding claims, which is chemically modified.  
 8. An Interleukin-2 receptor  $\gamma$ -chain polypeptide according to any of the preceding claims, which is modified by way of acetylation and/or amidation and/or treatment with polyethylene.  
 50 9. A DNA sequence coding for a polypeptide according to any of the claims 1 to 6.  
 10. A DNA sequence according to claim 9, which is represented by the following nucleotide sequence:  
 (Seq. Id. No. 7)

5 CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT 48  
 GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT 96  
 CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG 144  
 AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT 192  
 CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC 240  
 AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA 288  
 AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC 336  
 CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT 384  
 10 CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT 432  
 GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT 480  
 TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT 528  
 GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT 576  
 GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC 624  
 TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG 672  
 15 GGG AGC AAT ACT TCA AAA TAG 693

11. A DNA sequence according to claim 9, which is represented by the following nucleotide sequence:  
 (Seq. Id. No. 6)

20  
 25 ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG 48  
 CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG 96  
 AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC 144  
 TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG 192  
 TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC 240  
 CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT 288  
 GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT 336  
 TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT 384  
 GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG 432  
 30 ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA 480  
 ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC 528  
 AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC 576  
 TGG GAC CAC AGC TGG ACT GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC 624  
 TCC TTG CCT AGT GTG GAT GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG 672  
 35 AGC CGC TTT AAC CCA CTC TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG 720  
 AGC CAC CCA ATC CAC TGG GGG AGC AAT ACT TCA AAA TAG 759

12. A DNA sequence according to claim 9, which is represented by the following nucleotide sequence:  
 (Seq. Id. No. 5)

45 CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG AAT GAA GAC ACC ACA GCT 48  
 GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC TCC CTC AGC GTT TCC ACT 96  
 CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG TTC AAT GTC GAG TAC ATG 144  
 AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT 192  
 AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC CAG CCT ACC AAC CTC ACT 192  
 CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT GAT AAA GTC CAG AAG TGC 240  
 AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT TCT GGC TGT CAG TTG CAA 288  
 AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT GTT GTT CAG CTC CAG GAC 336  
 50 CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG ATG CTA AAA CTG CAG AAT 384  
 CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA ACA CTT CAC AAA CTG AGT 432  
 GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC AGA TTC TTG AAC CAC TGT 480  
 TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC TGG GAC CAC AGC TGG ACT 528  
 GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC TCC TTG CCT AGT GTG GAT 576  
 55 GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG AGC CGC TTT AAC CCA CTC 624  
 TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG AGC CAC CCA ATC CAC TGG 672  
 GGG AGC AAT ACT TCA AAA GAG AAT CCT TTC CTG TTT GCA TTG GAA GCC 720

GTG GTT ATC TCT GTT GGC TCC ATG GGA TTG ATT ATC AGC CTT CTC TGT 768  
 GTG TAT TTC TGG CTG GAA CGG ACG ATG CCC CGA ATT CCC ACC CTG AAG 816  
 AAC CTA GAG GAT CTT GTT ACT GAA TAC CAC GGG AAC TTT TCG GCC TGG 864  
 AGT GGT GTG TCT AAG GGA CTG GCT GAG AGT CTG CAG CCA GAC TAC AGT 912  
 5 GAA CGA CTC TGC CTC GTC AGT GAG ATT CCC CCA AAA GGA GGG GCC CTT 960  
 GGG GAG GGG CCT GGG GCC TCC CCA TGC AAC CAG CAT AGC CCC TAC TGG 1008  
 GCC CCC CCA TGT TAC ACC CTA AAG CCT GAA ACC TGA 1044

- 10 13. A DNA sequence according to claim 9, which is represented by the following nucleotide sequence:  
 (Seq. Id. No. 4)

15 ATG TTG AAG CCA TCA TTA CCA TTC ACA TCC CTC TTA TTC CTG CAG CTG 48  
 CCC CTG CTG GGA GTG GGG CTG AAC ACG ACA ATT CTG ACG CCC AAT GGG 96  
 AAT GAA GAC ACC ACA GCT GAT TTC TTC CTG ACC ACT ATG CCC ACT GAC 144  
 TCC CTC AGC GTT TCC ACT CTG CCC CTC CCA GAG GTT CAG TGT TTT GTG 192  
 TTC AAT GTC GAG TAC ATG AAT TGC ACT TGG AAC AGC AGC TCT GAG CCC 240  
 CAG CCT ACC AAC CTC ACT CTG CAT TAT TGG TAC AAG AAC TCG GAT AAT 288  
 20 GAT AAA GTC CAG AAG TGC AGC CAC TAT CTA TTC TCT GAA GAA ATC ACT 336  
 TCT GGC TGT CAG TTG CAA AAA AAG GAG ATC CAC CTC TAC CAA ACA TTT 384  
 GTT GTT CAG CTC CAG GAC CCA CGG GAA CCC AGG AGA CAG GCC ACA CAG 432  
 ATG CTA AAA CTG CAG AAT CTG GTG ATC CCC TGG GCT CCA GAG AAC CTA 480  
 ACA CTT CAC AAA CTG AGT GAA TCC CAG CTA GAA CTG AAC TGG AAC AAC 528  
 AGA TTC TTG AAC CAC TGT TTG GAG CAC TTG GTG CAG TAC CGG ACT GAC 576  
 25 TGG GAC CAC AGC TGG ACT GAA CAA TCA GTG GAT TAT AGA CAT AAG TTC 624  
 TCC TTG CCT AGT GTG GAT GGG CAG AAA CGC TAC ACG TTT CGT GTT CGG 672  
 AGC CGC TTT AAC CCA CTC TGT GGA AGT GCT CAG CAT TGG AGT GAA TGG 720  
 AGC CAC CCA ATC CAC TGG GGG AGC AAT ACT TCA AAA GAG AAT CCT TTC 768  
 CTG TTT GCA TTG GAA GCC GTG GTT ATC TCT GTT GGC TCC ATG GGA TTG 816  
 30 ATT ATC AGC CTT CTC TGT TTG GAG CAC TTG GTG TAT TTC TGG CTG GAA CGG ACG ATG CCC 864  
 CGA ATT CCC ACC CTG AAG AAC CTA GAG GAT CTT GTT ACT GAA TAC CAC 912  
 GGG AAC TTT TCG GCC TGG AGT GGT GTG TCT AAG GGA CTG GCT GAG AGT 960  
 CTG CAG CCA GAC TAC AGT GAA CGA CTC TGC CTC GTC AGT GAG ATT CCC 1008  
 CCA AAA GGA GGG GCC CTT GGG GAG GGG CCT GGG GCC TCC CCA TGC AAC 1056  
 CAG CAT AGC CCC TAC TGG GCC CCC CCA TGT TAC ACC CTA AAG CCT GAA 1104  
 35 ACC TGA 1110

- 40 14. A DNA sequence according to any of the claims 9 to 13, which has an altered nucleotide sequence due to the degeneracy of the genetic code, point mutations, induced mutations or represents an allelic variant thereof.

15. A vector including a DNA-sequence according to any of the claims 9 to 14.

- 45 16. A vector according to claim 15, which is an expression vector.

17. A vector according to claims 15 or 16, which can be propagated in an eucaryotic cell.

18. A vector according to claims 15 or 16, which can be propagated in an procaryotic cell.

- 50 19. A cell transformed with a DNA-sequence according to any of the claims 9 to 14.

20. A cell transformed with a vector according to any of the claims 15 to 17.

- 55 21. A cell according to claim 19 or 20, which is an eucaryotic cell.

22. A cell according to claim 19 or 20, which is an procaryotic cell.



23. A cell according to claim 21, which is a CHO cell.
24. A cell according to claim 21, which is a mouse L929 cell.
- 5 25. A cell according to claim 22, which is of the genus *E. coli*.
26. A cell according to claim 20, which is [FERM BP-4199].
27. A cell according to claim 20, which is [FERM BP-4200].
- 10 28. A method for the production of an Interleukin-2 receptor  $\gamma$ -chain polypeptide, comprising,  
culturing a cell according to any of the claims 18 to 26, and  
isolating said Interleukin-2 receptor  $\gamma$ -chain polypeptide.
- 15 29. A method for the production of an Interleukin-2 receptor  $\gamma$ -chain polypeptide according to claim 28,  
wherein the Interleukin-2 receptor  $\gamma$ -chain polypeptide is the human Interleukin-2 receptor  $\gamma$ -chain  
polypeptide.
30. An antibody, capable of binding to a polypeptide according to any of the claims 1 to 8.
- 20 31. An antibody according to claim 30, which is a monoclonal antibody.
32. A pharmaceutical composition, including a polypeptide according to any of the claims 1 to 8.
- 25 33. A pharmaceutical composition, including an antibody according to any of the claims 29 to 30.
34. A pharmaceutical composition according to any of the claims 32 to 33, which comprises a pharmaceuti-  
cal acceptable carrier.
- 30 35. Use of a pharmaceutical composition according to any of the claims 32 to 34 as an immune regulatory  
agent.
36. A method for the assay or detection of a gene encoding IL-2 receptor  $\gamma$ -chain polypeptide in a sample  
using a DNA sequence according to any of the claims 9 to 14.
- 35 37. A method for the assay or detection of a gene encoding IL-2 receptor  $\gamma$ -chain polypeptide in a sample  
using an antibody according to any of the claims 30 to 31.

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[Figures]

Fig. 1

Probe No. 1

```

ATACTGACGC CGAATGG
  TT A  A  A
    C    T  T
        C  C
    
```

Probe No. 2

```

ATACTGACGC CGAACGG
  TT A  A  A
    C    T  T
        C  C
    
```

Probe No. 3

```

ATACTTACGC CGAATGG
  T  C  A  A
    C    T  T
        C  C
    
```

Probe No. 4

```

ATACTTACGC CGAACGG
  T  C  A  A
    C    T  T
        C  C
    
```

Probe No. 5

```

AAAAAAAAAGA GGGCCTAGGC GC
      GG AT CAT
        T  T
        C  C
    
```

Probe No. 6

```

AAGAAAAAGA GGGCCTAGGC GC
      GG AT CAT
        T  T
        C  C
    
```

Fig. 2

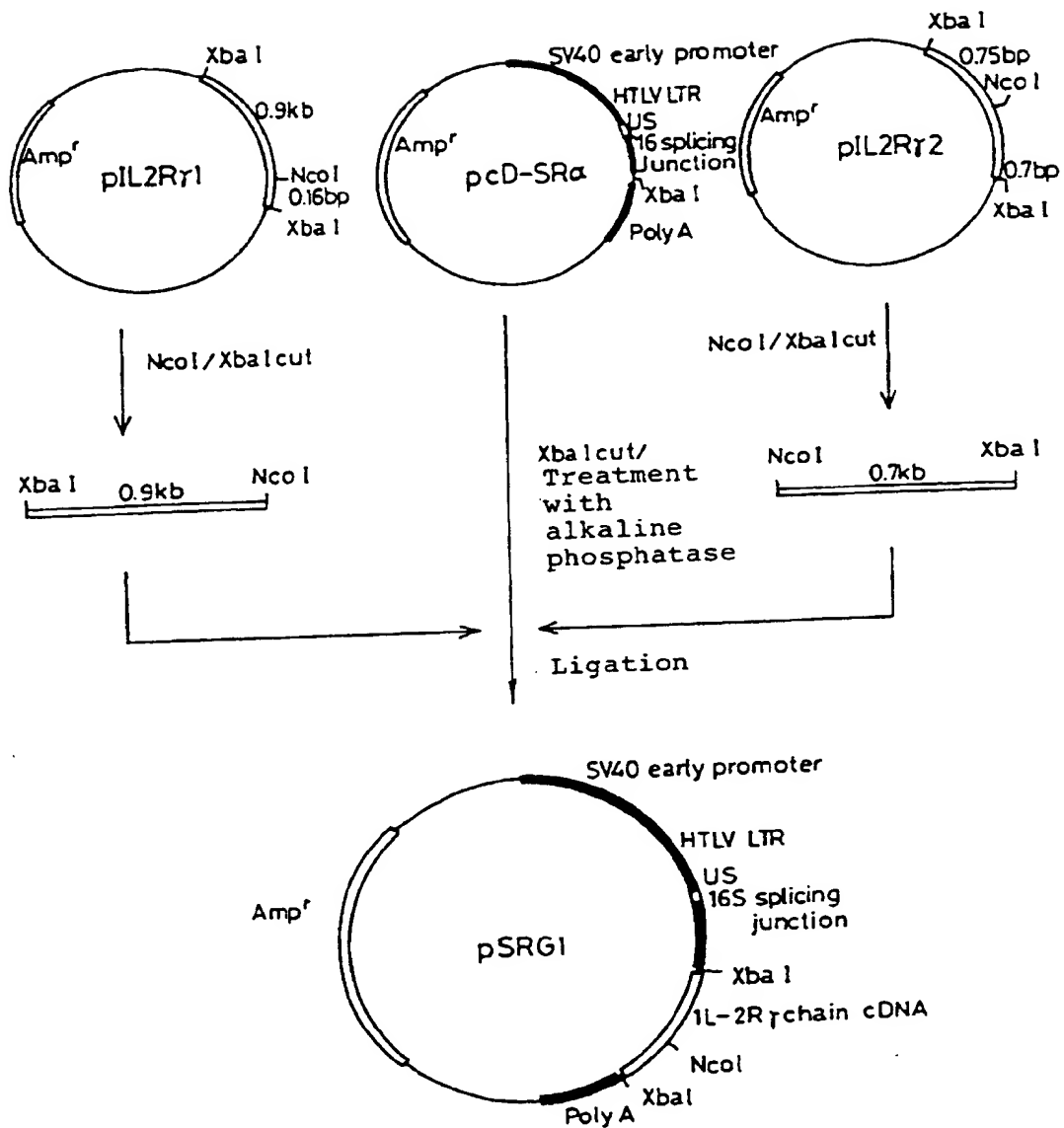
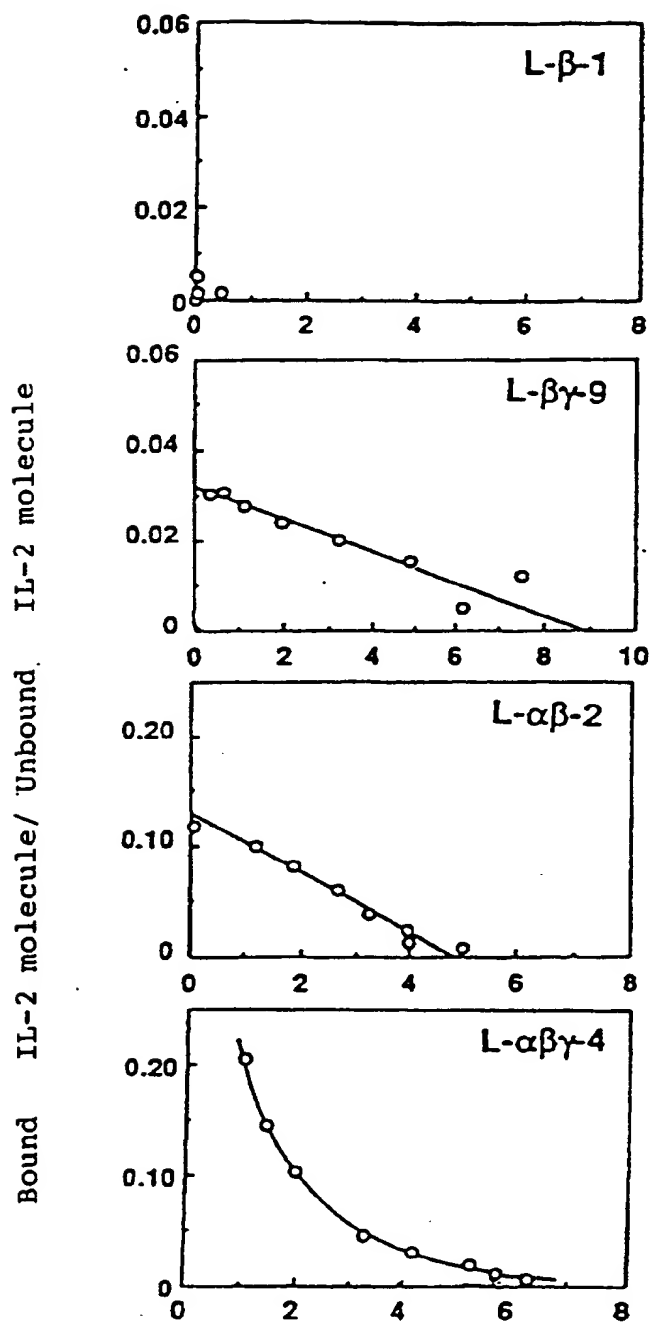
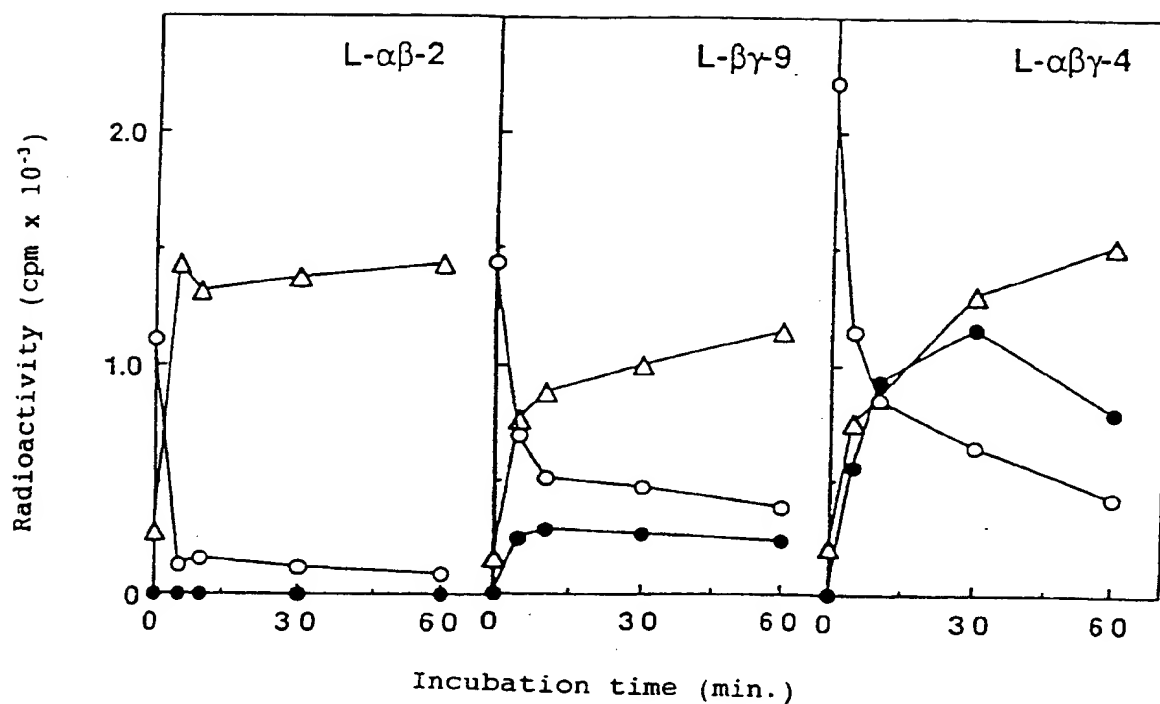


Fig. 3



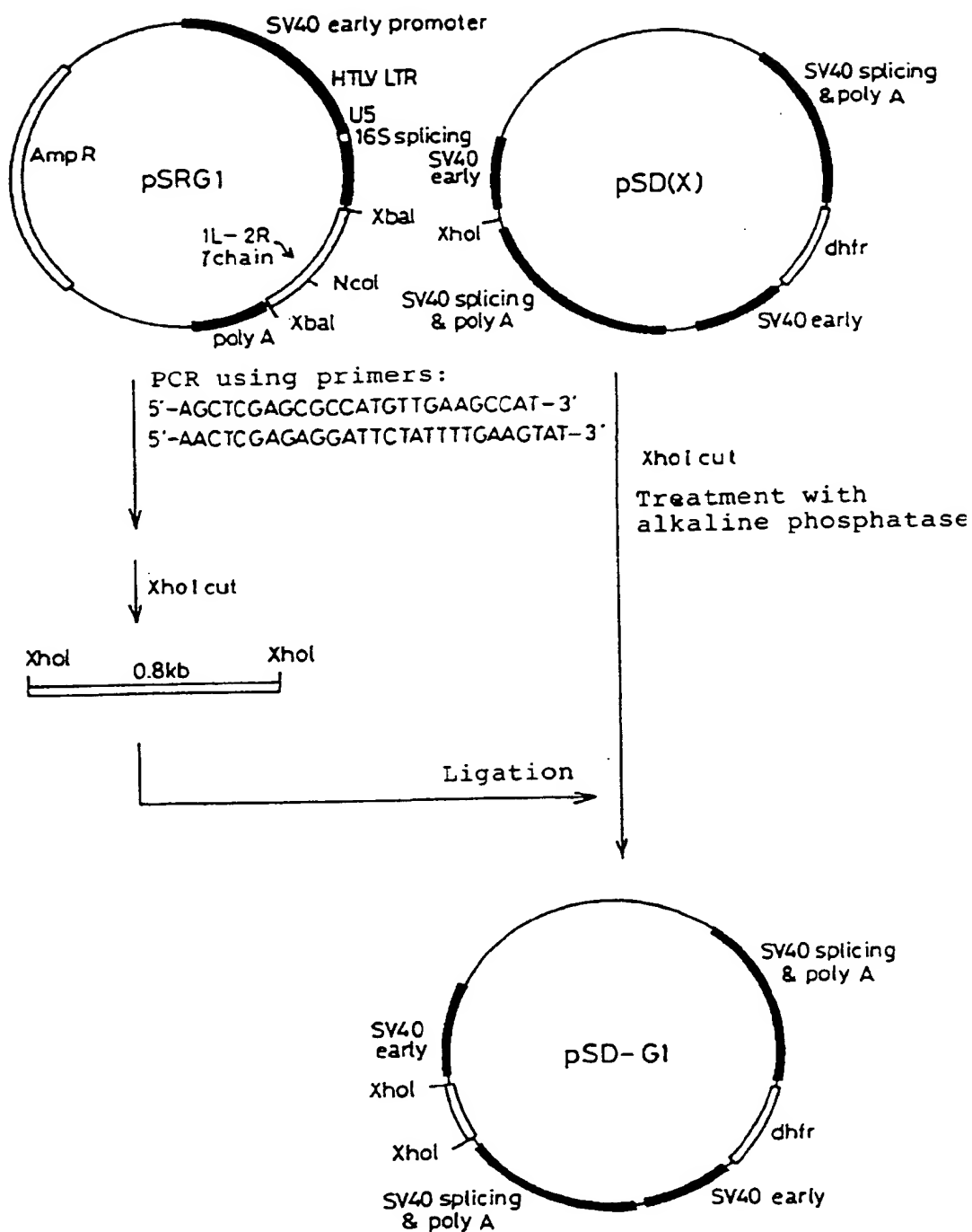
Number of bound IL-2 molecules per cell (X 10<sup>3</sup>)

Fig. 4



- $\Delta$ - $\Delta$ -: Radioactivity of IL-2 scraped off from cells during incubation at 37°C.
- $\bullet$ - $\bullet$ -: Radioactivity of IL-2 scraped off from cells by washing with glycine buffer.
- $\circ$ - $\circ$ -: Radioactivity of IL-2 bonded to cells even after washing with glycine buffer.

Fig. 5



(19)



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(54) **IL-2 receptor gamma chain molecule.**

(57) The present invention relates to an IL-2 receptor  $\gamma$  chain molecule, a DNA-sequence encoding the IL-2 receptor  $\gamma$  chain molecule, a vector possessing said DNA-sequence, a cell transformed with said vector, a method for the production of an IL-2 receptor  $\gamma$  chain molecule by culturing of said cell, an immune response regulatory agent comprising an IL-2 receptor  $\gamma$  chain molecule and an antibody to an

IL-2 receptor  $\gamma$  chain molecule.

Both the IL-2 receptor  $\gamma$  chain molecule and the antibody to the IL-2 receptor  $\gamma$  chain molecule are very useful immune response regulatory agents.

EP 0 578 932 A3



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## EUROPEAN SEARCH REPORT

Application Number  
EP 93 10 6561

DOCUMENTS CONSIDERED TO BE RELEVANT			
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A	EMBO JOURNAL. vol. 9, no. 12 , 1990 , EYNSHAM, OXFORD GB pages 3899 - 3905 ZURAWSKI, SANDRA M.; IMLER, JEAN LUC; ZURAWSKI, GERARD; 'Partial agonist/antagonist mouse interleukin-2 proteins indicate that a third component of the receptor complex functions in signal transduction' * the whole document *	1-37	
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Place of search THE HAGUE		Date of completion of the search 2 March 1994	Examiner Nauche, S
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## EUROPEAN SEARCH REPORT

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A	LYMPHOKINE RESEARCH vol. 9, no. 4, 1990 pages 539 - 542 SUGAMURA, KAZUO; TAKESHITA, TOSHIKAZU; ASAO, HIRONOBU; KUMAKI, SATORU; OHBO, KAZUYUKI; OHTANI, KIYOSHI; NAKAMURA, MASATAKA; 'IL-2-induced signal transduction: involvement of tyrosine kinase and IL-2 receptor .gamma. chain' * the whole document * -----	1-37
The present search report has been drawn up for all claims		
Place of search	Date of completion of the search	Examiner
THE HAGUE	2 March 1994	Nauche, S
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document		

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